

Charles University in Prague  
Faculty of Pharmacy in Hradec Králové

Department of pharmaceutical chemistry

„ELECTROSYNTHESIS OF DELTA-VALERO  
LACTONES“

„ELEKTROSYNTÉZA DELTA-VALEROLAKTONŮ“

Rigorous thesis

Mgr. Lenka Pochopová

Hradec Králové 2010

This work was carried out at the department of Pharmaceutical Chemistry, Charles University in Prague, Faculty of Pharmacy in Hradec Králové during the cooperation with department of Organic Chemistry, University of Alcalá under the supervision of Ing. Vladimír Kubíček, CSc.

### **Fair declaration**

I declare that I made this diploma thesis myself and mentioned every used source and used literature.

Date:

Signature:

**I thank to Ing.Vladimír Kubíček, CSc. for his advices, vasty help, needful support and good reminds.**

# CONTENTS:

1. ABSTRACT .....	7
1.1 SOUHRN.....	9
2. INTRODUCTION .....	11
3. THEORETICAL PART .....	14
3.1 TYPES OF ELECTROLYSIS.....	15
3.2 CYCLIC VOLTAMMETRY .....	17
3.3. LACTONES .....	22
4. EXPERIMENTAL PART .....	26
4.1 INSTRUMENTAL.....	27
4.2 LIST OF CHEMICALS .....	28
4.3 CYCLIC VOLTAMMETRY .....	29
4.4 ELECTROLYSIS WITH DRY ACETONITRILE/LICLO <sub>4</sub> AS SSE: .....	30
4.4.1 ELECTROSYNTHESIS OF 3, 3-DICHLORO-4-HYDROXY-5,5-DIMETHYL- TETRAHYDROPYRAN-2-ONE.....	30
4.5 GENERAL PROCEDURE FOR THE ELECTROCHEMICAL REDUCTION IN DICHLOROMETHANE.....	31
4.5.1 ELECTROSYNTHESIS OF 3, 3-DICHLORO-4-HYDROXY-5,5-DIMETHYL- TETRAHYDROPYRAN-2-ONE.....	31
4.5.2 ELECTROSYNTHESIS OF 3,3 – DICHLORO - 5,5 – DIETHYL -4- HYDROXYTETRAHYDROPYRAN-2-ONE.....	32
4.5.3 ELECTROSYNTHESIS OF 3,3 – DICHLORO - 5,5 – DIETHYL -4- HYDROXYTETRAHYDROPYRAN-2-ONE AND 3-CHLORO-5,5 – DIETHYL -4- HYDROXY-5,6- DIHYDROPYRAN -2- ONE.....	32
4.5.4 ELECTROSYNTHESIS OF 3, 3- DICHLORO-4-HYDROXY-5-METHYL-5-PHENYL- TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5-METHYL-5-PHEYNL-5,6- DIHYDROPYRAN-2-ONE .....	33
4.5.5 ELECTROSYNTHESIS OF 3,3-DICHLORO-4-HYDROXY-5,5-DIMETHYL- TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5,5-DIMETHYL-5,6- DIHYDROPYRAN-2-ONE .....	34
4.5.6 ELECTROSYNTHESIS OF 3,3-DICHLORO-4-HYDROXY-5-METHYL-5-PROPYL- TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5-METHYL-5-PROPYL-5,6- DIHYDROPYRAN-2-ONE .....	35
4.5.7 ELECTROSYNTHESIS OF 3,3-DICHLORO-5-BUTHYL-5-ETHYL-4- HYDROXYTETRAHYDROPYRAN-2-ONE OR 3-CHLORO-5-BUTHYL-5-ETHYL-4- HYDROXY-5,6-DIHYDROPYRAN-2-ONE.....	35

5. RESULTS AND DISCUSION.....	36
5.1 ELECTROLYSIS WITH DRY ACETONITRILE/LICLO <sub>4</sub> AS SSE: .....	37
5.1.1 ELECTROSYNTHESIS OF 3, 3-DICHLORO-4-HYDROXY-5,5-DIMETHYL- TETRAHYDROPYRAN-2-ONE.....	37
5.2 ELECTROLYSIS WITH DRY DICHLOROMETHANE/TEACL AS SSE: .....	38
5.2.1 ELECTROSYNTHESIS OF 3, 3-DICHLORO-4-HYDROXY-5, 5-DIMETHYL- TETRAHYDROPYRAN-2-ONE.....	38
5.2.2 ELECTROSYNTHESIS OF 3, 3 – DICHLORO - 5,5 – DIETHYL -4- HYDROXYTETRAHYDROPYRAN-2-ONE.....	39
5.2.3 ELECTROSYNTHESIS OF 3, 3 – DICHLORO - 5,5 – DIETHYL -4- HYDROXYTETRAHYDROPYRAN-2-ONE OR 3-CHLORO-5, 5 – DIETHYL -4- HYDROXY-5,6- DIHYDROPYRAN -2- ONE.....	39
5.2.4 ELECTROSYNTHESIS OF 3, 3- DICHLORO-4-HYDROXY-5-METHYL-5-PHENYL- TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5-METHYL-5-PHEYNL-5,6- DIHYDROPYRAN-2-ONE .....	43
5.2.5 ELECTROSYNTHESIS OF 3,3-DICHLORO-4-HYDROXY-5,5-DIMETHYL- TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5,5-DIMETHYL-5,6- DIHYDROPYRAN-2-ONE .....	48
5.2.6 ELECTROSYNTHESIS OF 3, 3-DICHLORO-4-HYDROXY-5-METHYL-5-PROPYL- TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5-METHYL-5-PROPYL-5,6- DIHYDROPYRAN-2-ONE .....	52
5.2.7 ELECTROSYNTHESIS OF 3,3-DICHLORO-5-BUTHYL-5-ETHYL-4- HYDROXYTETRAHYDROPYRAN-2-ONE OR 3-CHLORO-5-BUTHYL-5-ETHYL-4- HYDROXY-5,6-DIHYDROPYRAN-2-ONE.....	56
5.3 OVERAL DISCUSION: .....	61
6. CONCLUSION .....	67
7. LIST OF ABBREVIATIONS .....	69
8. LITERATURE .....	71

# **1.ABSTRACT**

## ABSTRACT

Charles University in Prague

Faculty of Pharmacy in Hradec Králové

Department of pharmaceutical chemistry

Candidate: Mgr. Pochopová Lenka

Consultant: Ing. Kubíček Vladimír, CSc.

Title of Thesis: „ELECTROSYNTHESIS OF DELTA-VALERO LACTONES”

In this project electrolysis has been used as a method for a synthesis of new compounds. The main aim is cathodic reduction of the carbon-chlorine bond in a series of aldol trichloroacetates. Formed carbanion would form a 6 member ring by attaching the carbonyl group. Two structures can be formed:  $\alpha$ ,  $\alpha$ -dichloro- $\beta$ -hydroxy- $\delta$ -lactones and  $\alpha$ ,  $\beta$ -unsaturated- $\alpha$ -chloro- $\delta$ -lactones from the starting esters using electrolysis. The whole process was performed at controlled potential in a separated cell, on mercury pool as a cathode and platinum as an anode in an argon atmosphere with dichloromethane/tetraethylammonium system. During the process two electrons have been passed. The synthesized lactones are completely new compounds. In this report also electrochemical and spectroscopy properties of those compounds have been characterized to provide for their other use.



## **1.1 SOUHRN**

## ABSTRAKT

Univerzita Karlova v Praze

Farmaceutická fakulta v Hradci Králové

Katedra farmaceutické chemie

Kandidát: Mgr. Pochopová Lenka

Konzultant: Ing. Kubíček Vladimír, CSc.

Název rigorózní práce: „ELEKTROSYNTÉZA DELTA-VALEROLAKTONŮ”

Tato práce popisuje využití elektrolýzy pro syntézu nových sloučenin. Hlavním cílem je katodická redukce vazeb uhlík-chlor ve skupině esterů kyseliny trichloroctové s aldoly. Touto reakcí vznikají dva možné produkty:  $\alpha,\alpha$ -dichloro- $\beta$ -hydroxy- $\delta$ -laktony a  $\alpha,\beta$ -nenasycené- $\alpha$ -chloro- $\delta$ -lactony. Celý proces probíhá pod kontrolovaným napětím v oddělených celách na rtuťové kapce tvořící katodu a za použití platiny jako anody, to vše v atmosféře argonu. Elektrolýt je tvořen systémem dichloromethan/ tetraethylamonium chlorid. Během reakce dochází k přesunu dvou elektronů. Vzniklé laktony jsou naprosto nové sloučeniny. V práci dále uvádím některé elektrochemické a spektroskopické vlastnosti získaných sloučenin.

## **2. INTRODUCTION**

This project is a continuation of my diploma thesis<sup>1</sup>, which described the synthesis of esters of trichloroacetic acid with aldols starting from commercial aldehydes. The esters have carbon-chlorine bonds and that is why they are suitable materials for other reactions especially for electrolysis. This is the main aim of the work of the group of electro-organic chemistry at the Department of organic chemistry of the University of Alcalá, led by Prof. Dr. Fructuoso Barba. One of the preferred topics studied by this research group is the electrochemical behaviour of the carbon-halogen-bond in organic compounds. It leads to the synthesis of a wide variety of important compounds with excellent yields. It includes epoxides, diketones, 3, 6- diarylpyridazines, cyclopropenes or regioselective synthesis of enolic carbonates, etc. One of the most studied process was the reduction of phenylacyl bromide in aprotic medium (DMF/ LiClO<sub>4</sub>) obtaining 2, 4-diarylfuranes in 80 % yield. 3-chloro-4-alkyl (-aryl) coumarines<sup>2</sup> or 1-alkyl-4-alkyl (-aryl)-3-chloroquinolinones were another type of the obtained heterocycles. They can be easily prepared by cathodic reduction of the trichloroacetylesters of o-hydroxyphenones or o-(N-alkyl) aminophenones.<sup>3</sup> Their work and experiences put the ground of my project.

Luigi Galvani got electrochemistry started in the mid 1780s. During his experiments with frog legs he discovered the contraction of the muscle influenced by static electricity. This was the primer building stone for the discovery of electrochemical cells.

In the course of year 1793 the Italian physicist Alessandro Volta discovered that electricity could be produced by situating two dissimilar metals on opposite side of a moistened paper. He worked out the electrochemical serial of metals.

Organic electrochemistry, which my thesis deals with, was emerged in 1836 by Michael Faraday, when he observed the release of a gas by passing current through acetate solutions.

Electrochemistry exploits the movement of ionic particles. The character of these ionic particles was explained by the theory of ions by Svante Arrhenius in 1884. He postulated that salts in their solutions not being existent as molecules but as smaller positively and negatively charged particles. This theory encountered resistance and the character of ions could not be justified until the clearing of the atomic construction.

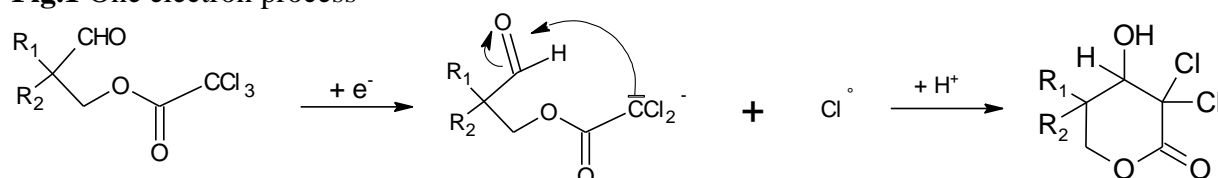
General conventional chemistry gives that a redox reaction is a transfer of electrons between two reagents. In electrochemical processes the transfer occurs between the substrate and a metal electrode, usually inert, by means of the electric current.

Electrochemistry includes two types of processes: redox reaction produces current (batteries) and constant current can be used to carry out chemical reactions (electrolysis). The first case is represented by a spontaneous process, whereas in the second case the necessary potential is supplied by electric current. In this project only electrolytic processes are used.<sup>2</sup>

My point of view was focussed on the products of electrolysis, on their properties and also on conditions of reaction.

The previous studies of Barbra's group with trichloroacetates of hydroxyacetophenone<sup>3</sup>, in which coumarines were obtained, induced me to expect a one electron process. The electro generated anion attacks nucleophilically to the carbonyl group leading to the dichlorolactones (Fig.1).

**Fig.1** One electron process



### **3. THEORETICAL PART**

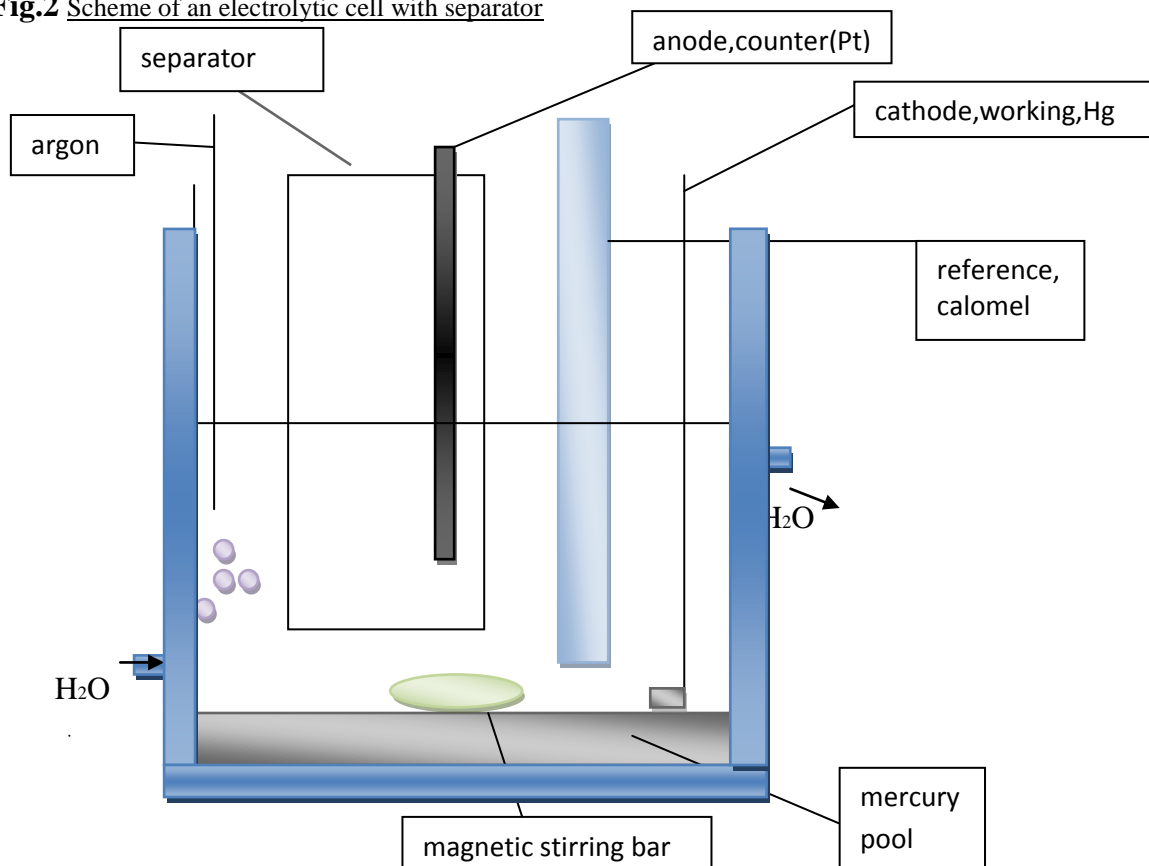
### **3.1 TYPES OF ELECTROLYSIS**

Two main ways can be used to carry out electrolysis:

- at a controlled potential
- at a constant current

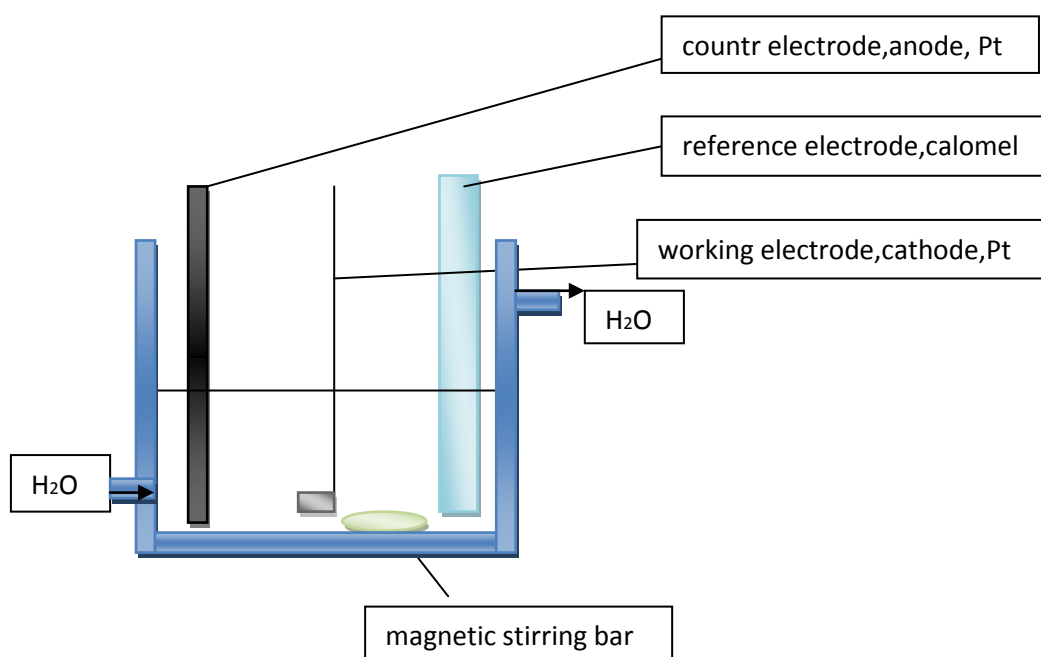
A cell with (Fig.2) or without separation (Fig.3) can be used during the electrolysis at a controlled potential. Because of the low conductivity of the organic compounds an electrolyte must be used in order to allow the current to pass. The solvent must be chosen having in mind that it has to dissolve both the organic compound and the electrolyte. It is very important to select the right solvent-supporting electrolyte system (SSE), which means the combination of solvent and electrolyte that supplies the best conditions required for every process. The potential, achieved by a certain electrode, varies depending on the SSE. The reference electrode is very often a calomel electrode (SCE) which should be placed the most closely to the working electrode.<sup>4</sup> Fig. 2 shows a cell with electrodes and separator for a reduction process, which I used during the electrolysis.

**Fig.2** Scheme of an electrolytic cell with separator



The counter and working electrode are separated by a glass tube with a glass frit at its bottom, impermeable for the organic compounds (separator), so as avoiding products, formed at one of the electrodes surface, get in contact with the other one. The SSE is added to both parts (cell, separator) in the same level of liquid. The substrate is added only in the liquid with working electrode. Fig. 3 shows cell without separation. The SSE and the substrate are added in the cell without membrane for separation. This cell is used when the reaction is carried out at constant current. But it is very complicated because many secondary products are formed during the process.

**Fig.3** Scheme of an electrolytic cell without separator



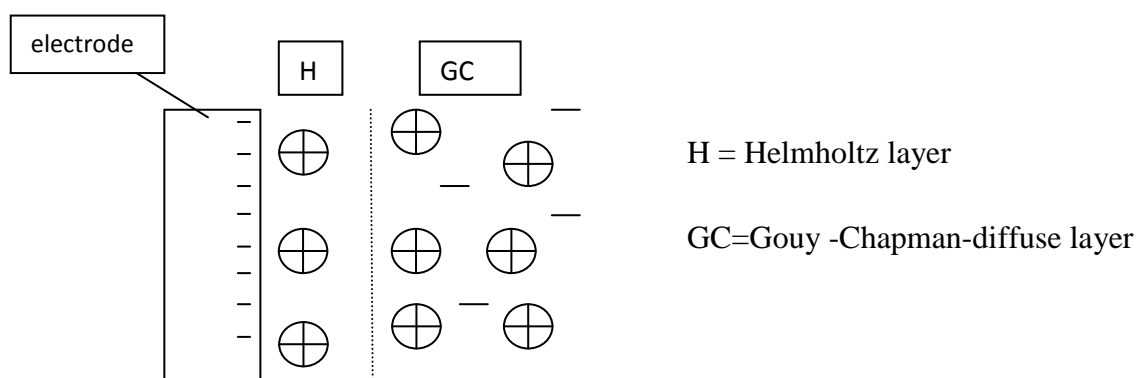
The controlled potential is equal to optimal potential for reduction of the compound. This potential can be analysed by cyclic voltammetry.



## 3.2 CYCLIC VOLTAMMETRY

In the early 20<sup>th</sup> century the newly developed technique of polarography was applied to organic molecules, but mainly in aqueous solution and with the focus on quantitative concentration analysis. The development of operational amplifiers, their use in the construction of potentiostats, and the conception of cyclic voltammetry as a mechanistic tool, however, provided the desired instrumental methodology and sparked a development which still continues.

In an electrochemical process an electron transfer (ET) occurs at the interface between an electrode (a conducting piece of matter usually composed of a metal or carbon) and an electrolyte (a conducting liquid phase). Consequently, electrochemistry is dealing with heterogeneous systems. The structure of this interface is a double layer (Fig.4).



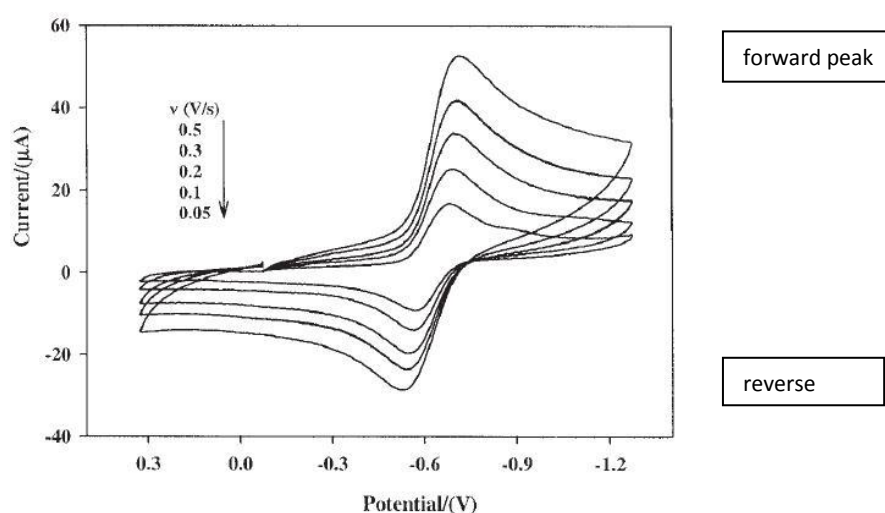
**Fig.4** Electric double layer

On the solution side it is defined by the formation of a Helmholtz layer of closely attached ions and a diffuse layer (Gouy-Chapman). An excess charge on the electrode is complemented by an excess of oppositely charged ions in the electrolyte. The exact composition of the electrochemical double layer depends on the potential difference between the electrode and the electrolyte.<sup>5</sup>

For a long time cyclic voltammetry has been largely used for the elucidation of electrode processes as well as for the quantitative determination of the kinetic and thermodynamic parameters characteristic of a given electrode process. In spite of contributions to the study of cyclic voltammetry at spherical electrodes which have been carried out both for solution soluble product and for amalgam formation in practice experimentalists prefer to develop their investigations at plane electrodes, or at spherical ones when curvature effects

have little importance, because when the time scale changes (the main tool for any kinetic study) it is difficult to discriminate between kinetic and curvature effects. However, it is evident that the apparent sphericity is given by the simultaneous contribution of the electrode radius and the time scale and, therefore, these contributions can be opposed and balanced.<sup>6</sup>

Cyclic voltammetry is one of the most widely used electro analytical techniques. It is based on scanning of working electrode during the experiment. The method is characterized by continuous increase of potential from the initial value to the terminal value and back to the starting point (Fig.5).



**Fig.5** Cyclovoltammogram

The time scale of the CV experiment can be easily varied through the potential scan rate:

$$v = dE/dt$$

Lower limits of  $v$  at microelectrodes are about 10mV/s, while at the upper limit 50V/s can be achieved. With UMEs scan rates up to  $10^6$  V/s have been reached. Commercial instruments typically allow 300 V/s. Since a scan extends over potential ranges of a few tenths of a volt to a few volts, a cycle is completed within a few minutes (low  $v$ ) or in less than a  $\mu\text{s}$  (high  $v$ ).

Consider a substrate susceptible to a simple ET without coupled chemical or adsorption steps. Upon scanning E, potentials are reached where the substrate undergoes a redox process. Governed by the Nernst equation (1),

$$E = E^{\circ} + \frac{RT}{nF} \ln \frac{C_{ox}(x=0)}{C_{red}(x=0)} \quad (1)$$

*E*-potential,  $E^{\circ}$ -starting potential,  $T$ -temperature,  $c_{ox}$ -concentration of oxidised form,  $c_{red}$ -concentration of reduced form,  $F$ -Faraday constant,  $n$ -number of changing electrons,  $R$ -gas constant.

The concentration of the substrate at  $x=0$  gradually decreases, inducing diffusion. Due to interplay between the increase of the concentration profile steepness caused by the potential variation (increasing current), and the relaxation of the profiles similar to chronoamperometric conditions (decreasing current), a peak shaped current–time of current-potential curve (forward peak) is recorded. If the product of the ET is stable, it remains present in the diffusion layer and can be transformed back to the starting compound upon reversal of the scan direction (reverse peak).

In this way, the stability of transient species and products can be assessed. The kinetics of their formation and further reaction(s) may be studied. Furthermore, cyclic voltammetry allows the resolution of redox processes at different potentials, and the determination of redox potentials associated with various oxidation states. Finally, the kinetics of the ET itself, as well as the presence, extent, and rate of adsorption processes are accessible.

A large number of examples have been accumulated in the literature over the years with many different reaction mechanisms coupled to the redox processes at the electrode. Depending on these mechanisms, shapes of cyclic voltammograms widely differ. Often, from a qualitative inspection, a mechanistic hypothesis is developed, which is then confirmed by the analysis of quantitative criteria (e.g. shift of peak potentials, variation of peak currents or peak current ratios with  $v$  and/or concentration. From such analyses already values for mechanistic parameters may be derived.

Full analysis of CV experiments, however, also includes the simulation of the current-potential curves. The concentration profiles and the voltammogram are calculated from equations describing transport, ET, chemical kinetics, and adsorption based on a mechanistic model of the processes and the assumption of kinetic, thermodynamic and /or transport parameters. Several public domain and commercial computer programs for the simulation of electrochemical experiments are available. Comparison to experiments (fitting) yields optimal values of these parameters. It is essential to analyze series of voltammograms recorded at various experimental conditions, in order to ensure a high quality of the estimated values.

Many researchers regard this technique now as a standard tool for the characterization of newly synthesized compounds.<sup>3</sup>

Cyclic voltammetry can be also used for the researching of the biological redox activity in living systems because redox processes are essential for the life of organisms. Therefore CV can provide information regarding the kinetics of the electron transfer step and in many cases even about the mechanism of redox changes in the studied systems. All processes that provide energy to organisms are sequences of redox reactions and can be defined as harvesting of reducing equivalents, e.g., compounds with low redox potential. In addition to redox-active compounds, which participate in metabolism, there are a large number of compounds with low redox potential in other parts of the cells as well. The ability of tissues and body fluids to reduce various exogenous compounds is well known and corresponds to the ability of particular tissues to cope with oxidative stress. Thus, many of the low molecular weight antioxidants (LMWA) which alter the susceptibility of the cell to cope with reactive oxygen species affect the cellular redox state (CRS). CRS has been increasingly recognized as a critical component of stress-induced cellular responses and diseases. Numerous signal transduction pathways have been demonstrated to be regulated by CRS. The effect of environmental or other stimuli as well as a variety of drugs on the cellular redox state can lead to various cellular events, including control of the cell cycle, programmed cell death, and the activation of cytokine and growth factor gene expression. The redox state in the living cell is kept under very tight regulation, analogous to the regulation of cellular pH values. A significant decrease in the redox state value may lead to pathological events and is defined as redosis. Similarly, an increase in this value above the normal range is defined

as oxidosis. Determination of the CRS and its modulation by redox-active drugs could lead to new avenues of therapy and might help to elucidate various disease states and clinical disorders. CV Despite the importance of this parameter it is not widely used in clinical settings.<sup>7</sup>

### **3.3. LACTONES**

In chemistry, a lactone is a cyclic ester which can be seen as the condensation product of an alcohol group -OH and a carboxylic acid group -COOH in the same molecule. It is characterized by a closed ring consisting of two or more carbon atoms and a single oxygen atom, with a ketone group =O in one of the carbons adjacent to the latter.<sup>8</sup>

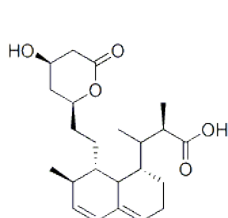
They can be made by organic reduction-esterification.<sup>9</sup> In halolactonization, an alkene is attacked by a halogen via electrophilic addition with the cationic intermediate captured intramolecularly by an adjacent carboxylic acid, for example<sup>10</sup>. A recent study has isolated  $\beta$ -lactones from bromination of 2, 3-dimethylmaleate and/or 2,3-dimethylfumarate disodium salts, under ambient and aqueous conditions. The carboxylate groups of the maleate and fumarate moieties exhibit neighbouring group effects and  $\alpha$ -lactones are proposed in the detailed mechanism.

The most stable structure for lactones are the 5-membered lactones ( $\gamma$ -lactone) and 6-membered lactones ( $\delta$ -lactone), because of the minimal angle strain in the compounds' structure.  $\gamma$ -lactones are so stable that, in the presence of dilute acids at room temperature, 4-hydroxy acids ( $R-CH(OH)-(CH_2)_2-COOH$ ) immediately undergo spontaneous esterification and cyclisation to the lactone.  $\beta$ -lactones do exist, but can only be made by special methods.  $\alpha$ -lactones can be detected as transient species in mass spectrometry experiments.<sup>11</sup> In this work mainly the  $\delta$ -lactones are discussed.

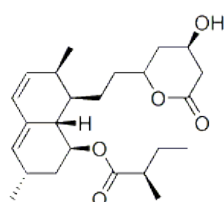
#### **Delta-Lactone**

The  $\delta$ -lactone moiety comprises structural subunits in a number of natural products, and substituted nonannulated  $\delta$ -lactones are important both as naturally occurring compounds and in synthetic applications. Unsaturated 5, 6 -dihydropyran-2-one derivatives substituted at the 6-position, found largely in plants and bacteria, display antifungal, antitumor, and cytotoxic activity.<sup>12</sup> These unsaturated  $\delta$ -lactones also have been reported as plant growth inhibitors and insect antifeedants,<sup>13</sup> while the saturated analogues are aroma constituents of fruit and meat products.<sup>14</sup> Saturated tetrahydropyran-2-ones are also found in compactin (Fig.6) and mevinolin (Fig.7) (cholesterol biosynthesis inhibitors)<sup>15</sup>, as prelactones which may serve as possible shunts in antitumor macrolide rhizoxin (Fig.8)<sup>16</sup>, in macrolide biosynthesis<sup>17</sup>, HMG-C-CoA reductase inhibitors<sup>18</sup> and the whitasteroids<sup>19</sup>. Rhizoxin reached

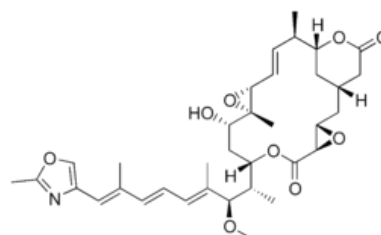
Phase II clinical trials for the treatment of ovarian, colorectal, renal, breast, and melanoma cancers.<sup>20</sup> It binds beta tubulin in eukaryotic cells disrupting microtubule formation. This, in turn, prevents formation of the mitotic spindle inhibiting cell division. Additionally rhizoxin can depolymerise assembled microtubules. The function of rhizoxin is similar to Vinca alkaloids.<sup>21</sup>



**Fig.6** Compactin

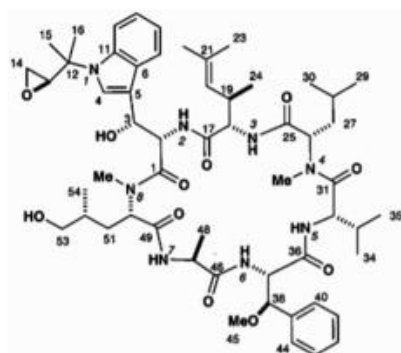


**Fig.7** Mevinolin



**Fig.8** Rhizoxin

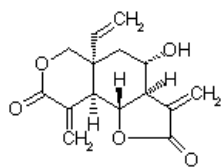
The  $\delta$ -lactones also play very important role in synthesis of  $\gamma$ ,  $\delta$ -unsaturated  $\alpha$ -amino acids (e.g. a nonproteinogenic amino acid contained in the potent anti-inflammatory agent cyclomarine A, Fig. 9).<sup>22</sup> Tetrahydropyran-2-ones have been employed in the synthesis of amino sugars<sup>23</sup>, the C16-C35 fragment of integramycin<sup>24</sup> and macrolides<sup>25</sup>.



**Fig.9** Cyclomarine A

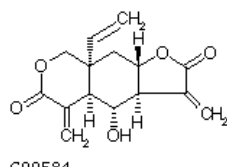
The  $\alpha$ -methylene- $\delta$ -lactone system can be found in several naturally occurring compounds such as vernolepin (Fig.10), vernomenin (Fig.11), pentalenolactone (Fig.12), teucriumlactone (Fig.13), artemisinin (Fig.14) and crassin (Fig.15). And have been shown to possess divers and potentially useful biological properties. The  $\alpha$ -methylene- $\delta$ -lactones are

also very attractive precursors for the preparation of a wide variety of compounds since they readily undergo conjugate additions, reduction of double bond, Diels-Alder reaction, 1,3-Michael-Claisen annulations, or cross methathesis.<sup>26</sup>



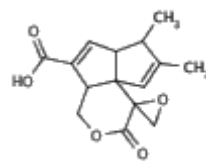
C09582

**Fig.10** Vernolepin

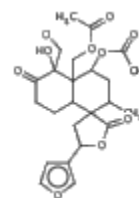


C09584

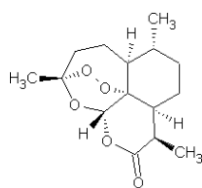
**Fig.11** Vernomenin



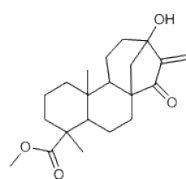
**Fig.12** Pentalenolactone



**Fig.13** Teucriumlactone



**Fig.14** Artemisinin

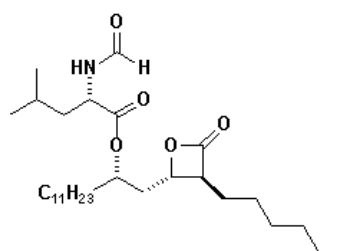


**Fig.15** Crassin

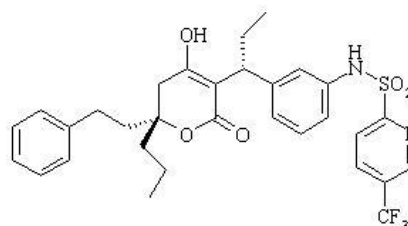
The Prelog-Djerassi lactone is an oxidative degradation product of several macrolide antibiotics and the many syntheses of this compound are illustrative of syntehtic approach to  $\delta$ -lactone.<sup>27</sup>

Substituted 3-hydroxy-  $\delta$ -lactones (3HLs) are valuable intermediates in the syntehtsis of paharmaceuticals and other biologically active natural products<sup>28</sup>. 3HLs are most prominent in the class of HMG-CoA reductase inhibitors known as statins, which are among the most potent cholesterol lowering drugs available and costitute five of the top 100 selling drugs<sup>29</sup>.

All approved statins have side chains comprising a 3HLs or the hydrolyzed 3, 5 –dihydroxycarboxylic acid analogue, which are essential for the bioactivity of statin drugs<sup>30</sup>. 3HLs have also been used in the synthesis of important drugs such as tetrahydrolipstatin (Fig.16), a lipase inhibitor prescribed for the tretment of obesity, and the antiretroviral agent tipranavir (Fig.17)<sup>31</sup>.



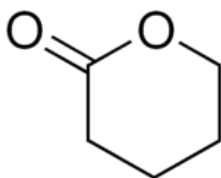
**Fig.16** Tetrahydrolipstatin



**Fig.17** Tipranavir



$\delta$  – Valerolactone (*Fig.18*) is found as a chemical intermediate in processes such as the production of polyesters.<sup>32</sup> Dihydropyrone derivatives have also biological activity against hepatitis C virus.<sup>33</sup>



**Fig.18**  $\delta$  -valero lactone

## **4. EXPERIMENTAL PART**

## **4.1 INSTRUMENTAL**

The electrolyses were carried out using Model 552 Amel potentiostat with Model 721 Amel electronic integrator.

The cyclovoltammetric curves were recorded on PGZ100 VoltaLab using a 0.1 M solution of  $\text{CH}_2\text{Cl}_2/\text{Et}_4\text{NCl}$  as SSE and Ag/ AgCl saturated (KCl 3 M) as the reference electrode and hanging mercury drop electrode as the working electrode.

IR measurements were performed on Model 583 Perkin-Elmer spectrophotometer; liquid samples were measured neat on NaCl plates; solid samples as KBr pellets.

$^1\text{H}$ -NMR (300 MHz) and  $^{13}\text{C}$ -NMR (300 MHz) spectra were recorded on Varian Unity 300 apparatus with deuteriochloroform as internal standard; the chemical shifts are given in ppm.

## 4.2 LIST OF CHEMICALS

1. All esters of trichloroacetic acid were synthesized earlier<sup>1</sup>.

2. Acetonitrile	$C_2H_3N_1$	Sigma-Aldrich
	Mr=41, 0	$d^{20}=0,79\text{g/cm}^3$
3. Carbon tetrachloride	$CCl_4$	Normasolv
	Mr=153, 82	$d^{20}=1,59\text{g/cm}^3$
4. Dichloromethane	$CH_2Cl_2$	Scharlau
	Mr=84, 93	$d^{20}=1,32\text{g/cm}^3$
5. Diethyl ether	$C_4H_{10}O$	Scharlau
	Mr=74, 12	$d^{20}=0,71\text{g/cm}^3$
6. Hexane	$C_6H_{14}$	Scharlau
	Mr=86, 18	$d^{20}=0, 67 \text{ g/cm}^3$
7. Chloroform D		Fluka
8. Lithium perchlorate	$LiClO_4$	Fluka
	Mr= 106, 39	
9. Magnesium sulphate anhydrous	$MgSO_4$	Panreac
	Mr=120, 37	
10. Tetraethyl ammonium chloride	$C_8H_{20}NCl$	Fluka
	Mr=165, 70	

### 4.3 CYCLIC VOLTAMMETRY

20 ml of a 0.1 M solution of  $\text{CH}_2\text{Cl}_2/\text{Et}_4\text{NCl}$  (0.1M  $\text{CH}_3\text{CN}/\text{LiClO}_4$ ) is placed into the cyclic voltammetry cell. A scan is carried out to 50mV/s from 0 up to -2 V, a blank signal being obtained this way, making sure of the electro active impurities nonexistence. 0.05mg of the product to be analyzed (Tab.1), is added and the same scan is carried out, being obtained this way a voltage/current graph that is typical of the analyzed compound. As soon as the sign is observed, the area where the reduction takes place is demarcated and a slower scan is realized, between 25 and 10 mV/s, to observe the reduction curve in a more detailed way. The reduction potential of the molecule corresponds with the irreversible reduction peak on the reduction curve.

**Tab.1** General conditions of the experiment

Scale of record	50 mV/ s	Reference electrode	Ag/ AgCL
Speed of dropping	300 mV/ s	Counter electrode	Graphite
Temperature	20°C	SSE	0.1M $\text{CH}_3\text{CN}/\text{LiClO}_4$ or 0.1M $\text{CH}_2\text{Cl}_2/\text{Et}_4\text{NCl}$
Sensibility	15 nA/ mm	Working electrode	Hanging mercury drop

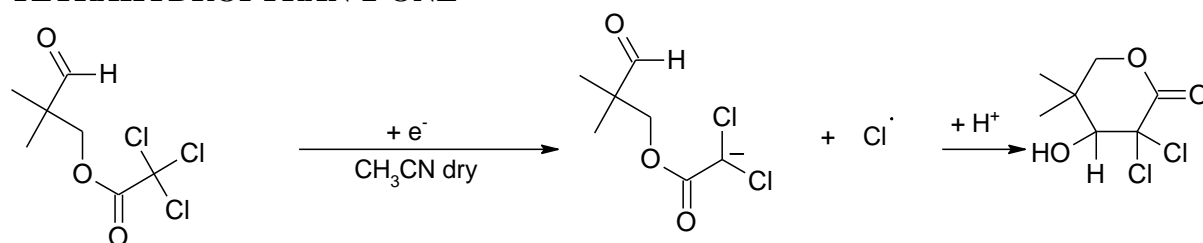
#### **4.4 ELECTROLYSIS WITH DRY ACETONITRILE/LICLO<sub>4</sub> AS SSE:**

General procedure for the electrochemical reduction in acetonitrile:

The reference electrode is a saturated calomel electrode (SCE), the anode is a platinum electrode with lithium perchlorate in dry acetonitrile as anolyte (SSE) and the cathode is a mercury pool with lithium perchlorate in dry acetonitrile and the respective educt as catholyte. The electrolysis cell is a divided cell, containing a piece of glass tubing with a glass of medium porosity (separator No. 4) at one end (anode compartment), equipped with magnetic stirrer and refrigerated with water to keep a constant temperature. Argon is added from a cylinder. It is led by tube with a small pipette at the end to the cathodic liquid, and the apparatus is covered with cotton.

All experiments were carried out at 20°C. Solid potassium carbonate is added to the anode compartment to neutralize the generated perchloric acid. The cathodic solution is filtered and the acetonitrile evaporated. The moiety is extracted with diethylether and distilled water. The organic phase is dried with MgSO<sub>4</sub> and the ether is evaporated.

##### **4.4.1 ELECTROSYNTHESIS OF 3, 3-DICHLORO-4-HYDROXY-5,5-DIMETHYL-TETRAHYDROPYRAN-2-ONE**



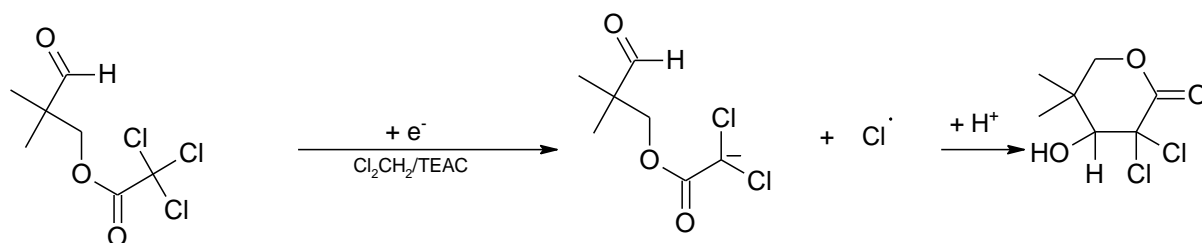
2.0 g (12.07 mmol) lithium perchlorate chloride is dissolved in 60.0 ml of dry acetonitrile. 20.0 ml is put in separator and 40.0 ml is used to dissolve 4mmol = 0.99 g of 2, 2-dimethyl-3-oxopropyl trichloroacetate.

The liquid level in the separator and in the cell should be same. When the electrolysis is terminated, the acetonitrile is evaporated and the moiety is extracted with diethylether. The organic phase is to be washed 5-6 times with distilled water (purifying of product = removing of salt).When any salt is removed it is dried with MgSO<sub>4</sub>, filtered and the ether is evaporated.

## **4.5 GENERAL PROCEDURE FOR THE ELECTROCHEMICAL REDUCTION IN DICHLOROMETHANE**

The reference electrode is a saturated calomel electrode (SCE), the anode is a platinum electrode with tetraethyl ammonium chloride (TEAC) in dry dichloromethane (SSE) as anolyte and the cathode is a mercury pool with tetraethylammonium chloride in dry dichloromethane and the respective compound as catholyte. The electrolysis cell is a divided cell, containing a piece of glass tubing with a glass of medium porosity (separator No. 4) at one end (anode compartment), equipped with magnetic stirrer, refrigerated with water to keep a constant temperature. Argon is added from cylinder led by tube with a small pipette at the end, which front to the cathodic liquid. The apparatus is covered with cotton. All experiments were carried out at 20°C. The cathodic solution is filtered and the dichloromethane evaporated. It is extracted with diethylether and washed with distilled water. The organic phase is dried with MgSO<sub>4</sub> and the ether is evaporated.

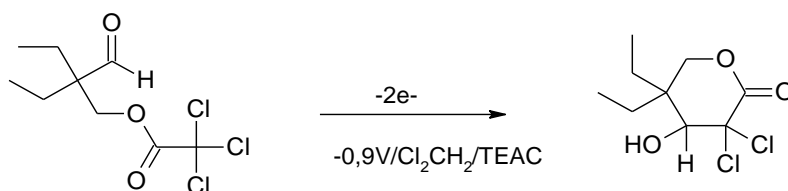
### **4.5.1 ELECTROSYNTHESIS OF 3, 3-DICHLORO-4-HYDROXY-5,5-DIMETHYL-TETRAHYDROPYRAN-2-ONE**



2.0 g (12.07 mmol) TEAC is dissolved in 60.0 ml of dry dichloromethane. 20.0 ml is put in separator and in 40.0 ml 4mmol = 0.99 g of 2, 2-dimethyl-3-oxopropyl trichloroacetate is dissolved.

The liquid level in separator and in cell should be the same. When the electrolysis is terminated, the dichloromethane is evaporated and the moiety is extracted with diethylether. The organic phase is to be washed 5-6 times with distilled water (purifying of product = removing of salt). When any salt is removed it is dried with MgSO<sub>4</sub>, filtered and the ether is evaporated.

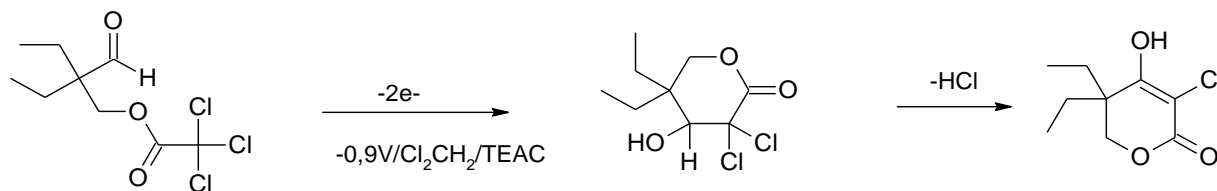
#### 4.5.2 ELECTROSYNTHESIS OF 3,3 - DICHLORO - 5,5 - DIETHYL -4-HYDROXYTETRAHYDROPYRAN-2-ONE



2.0 g (12.07 mmol) TEAC is dissolved in 60.0 ml of dry dichloromethane. 20.0 ml of the mixture is put in separator and in 40.0 ml 4mmol = 1.10 g of 2, 2-diethyl-3-oxopropyl trichloroacetate is dissolved.

The liquid level in separator and in cell should be the same. When the electrolysis is terminated, the dichloromethane is evaporated and the moiety extracted with diethylether. The organic phase is washed 5-6 times with distilled water (purifying of product = removing of salt). When the mixture is desalted it is dried with  $MgSO_4$ , filtered and the ether evaporated. If the product is solid, it is mixed with hexane and hexane evaporated (hexane dissolves impurities and cleans the product).

#### 4.5.3 ELECTROSYNTHESIS OF 3,3 - DICHLORO - 5,5 - DIETHYL -4-HYDROXYTETRAHYDROPYRAN-2-ONE AND 3-CHLORO-5,5 - DIETHYL -4-HYDROXY-5,6- DIHYDROPYRAN -2- ONE



2.0g (12.07 mmol) TEAC is dissolved in 60.0 ml of dry dichloromethane. 20.0 ml of the mixtures is put in separator and in 40.0 ml is dissolved 4mmol = 1.10 g of 2, 2- diethyl-3-oxopropyl trichloroacetate.



The liquid level in separator and in cell should be the same. When the electrolysis is terminated the catholyte is divided in to two parts.

The first part:

The first part is processed the same day as the electrolysis.

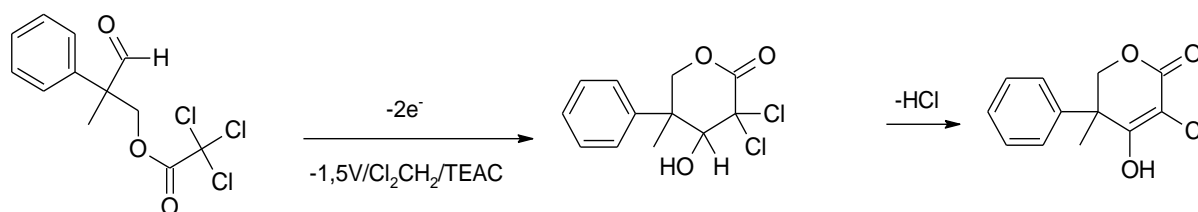
The dichloromethane is evaporated and the moiety is extract with diethylether. The organic phase is to be washed 5-6 times with distilled water (purifying of product = removing of salt).When it is without salt, it is dried with  $\text{MgSO}_4$  filtered and the ether is evaporated. If the product is solid it is mixed in hexane and hexane is evaporated (hexane dissolves impurities and cleans the product).

The second part:

The other part is put in the refrigerator for 12 hours and then the process is continued:

The dichloromethane is evaporated and the moiety is extracted with diethylether. The organic phase is to be washed 5-6 times with distilled water (purifying of product = removing of salt).When it is completely desalted, it is dried with  $\text{MgSO}_4$ , filtered and the ether is evaporated. If the product is solid, it is mixed with hexane and hexane is evaporated.

**4.5.4 ELECTROSYNTHESIS OF 3, 3- DICHLORO-4-HYDROXY-5-METHYL-5-PHENYL-TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5-METHYL-5-PHEYNL-5,6-DIHYDROPYRAN-2-ONE**

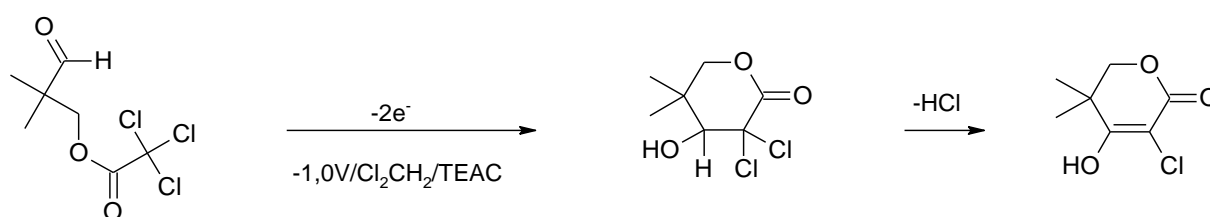


2.0g (12.07 mmol) TEAC is dissolved in 60.0 ml of dry dichloromethane. 20.0 ml are put in separator and in 40.0 ml is dissolved 4mmol = 1.24 g of 2-mehtyl-2-phenyl-3-oxopropyl trichloroacetate.

The liquid level in separator and in cell should be the same. When the electrolysis is terminated the catholyte is divided in to two parts.

Next process with both parts is same as in chapter 4.5.3

#### 4.5.5 ELECTROSYNTHESIS OF 3,3-DICHLORO-4-HYDROXY-5,5-DIMETHYL-TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5,5-DIMETHYL-5,6-DIHYDROPYRAN-2-ONE

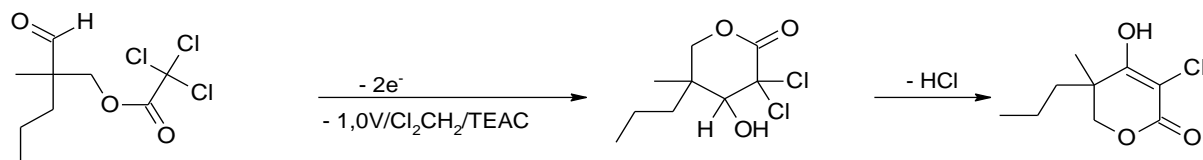


2.0g (12.07 mmol) TEAC is dissolved in 60.0 ml of dry dichloromethane. 20.0 ml are put in separator and in 40.0 ml is dissolved 4 mmol = 0.99 g of 2, 2- dimethyl-3-oxopropyl trichloroacetate.

The liquid level in separator and in cell should be the same. When the electrolysis is terminated the catholyte is divided in to two parts.

Next process with both parts is same as in chapter 4.5.3

#### 4.5.6 ELECTROSYNTHESIS OF 3,3-DICHLORO-4-HYDROXY-5-METHYL-5-PROPYL-TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5-METHYL-5-PROPYL-5,6-DIHYDROPYRAN-2-ONE

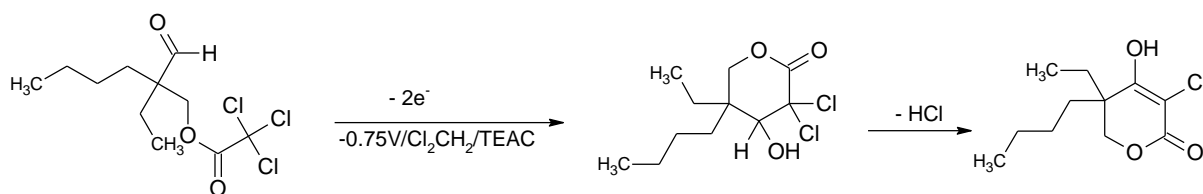


2.0g (12.07 mmol) TEAC is dissolved in 60.0 ml of dry dichloromethane. 20.0 ml are put in separator and in 40.0 ml is dissolved 4mmol = 1.10 g of 2- methyl-2-propyl-3-oxopropyl trichloroacetate.

The liquid level in separator and in cell should be the same. When the electrolysis is terminated the catholyte is divided in to two parts.

Next process with both parts is same as in chapter 4.5.3

#### 4.5.7 ELECTROSYNTHESIS OF 3,3-DICHLORO-5-BUTHYL-5-ETHYL-4-HYDROXYTETRAHYDROPYRAN-2-ONE OR 3-CHLORO-5-BUTHYL-5-ETHYL-4-HYDROXY-5,6-DIHYDROPYRAN-2-ONE



2.0g (12.07 mmol) TEAC is dissolved in 60.0 ml of dry dichloromethane. 20.0 ml are put in separator and in 40.0 ml is dissolved 4mmol = 1.24 g of 2- butyl-2-ethyl-3-oxopropyl trichloroacetate

The liquid level in separator and in cell should be the same. When the electrolysis is terminated the catholyte is divided in to two parts.

Next process with both parts is same as in chapter 4.5.3

## **5. RESULTS AND DISCUSSION**

## **5.1 ELECTROLYSIS WITH DRY ACETONITRILE/LICLO<sub>4</sub> AS SSE:**

I expected one electron transfer therefore in the preliminary electrolysis the current flow was interrupted after one Faraday per mol had passed through, once the intensity decreased considerably. The processes were initially performed using dry acetonitrile/LiClO<sub>4</sub> as SSE (system solvent-support electrolyte) at controlled potential of - 0,6V. The value of the controlled potential was taken from previous cyclic voltammetry experiments with the corresponding ester and the same SSE as in electrolysis.

### **5.1.1 ELECTROSYNTHESIS OF 3, 3-DICHLORO-4-HYDROXY-5,5-DIMETHYL-TETRAHYDROPYRAN-2-ONE**

Yield: 0.847 g = 3.98 mmol = 66%

#### **CV:**

Irreversible reduction peak – 0.65 V

The spectroscopy did not confirm the presence of the expected product.

The SSE showed not to be the suitable one for the process because the main product obtained was the dichloroacetate ester.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>, 300 K):

δ = 1.06 (s, 6H, CH<sub>3</sub>), 4.19 (s, 2H, CH<sub>2</sub>), 4.73 (s, 1H, CHOH) ppm.

**IR** (NaCl,  $\tilde{\nu}$ [cm<sup>-1</sup>])

$\nu$  = 3519.32 (OH), 2972.55 (C<sub>sp<sup>3</sup></sub>-H), 1764.83 (C=O, aldehyde).

The initially formed anion, instead of attacking to the carbonyl group as expected, withdraws a proton from the solvent.

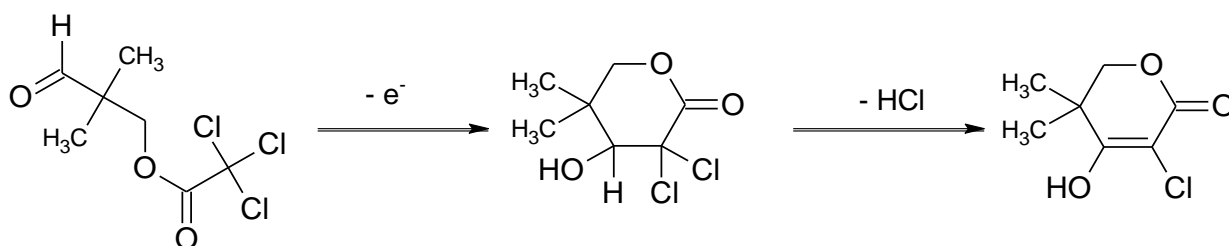
For this reason I changed the SSE to the following one: dichloromethane, tetraethylammonium chloride in which I performed completely the reaction 5.1.1 (see 5.2)

## **5.2 ELECTROLYSIS WITH DRY DICHLOROMETHANE/TEACL AS SSE:**

This modification showed better results, because dry dichloromethane is not so sensitive for air humidity and gives better results.

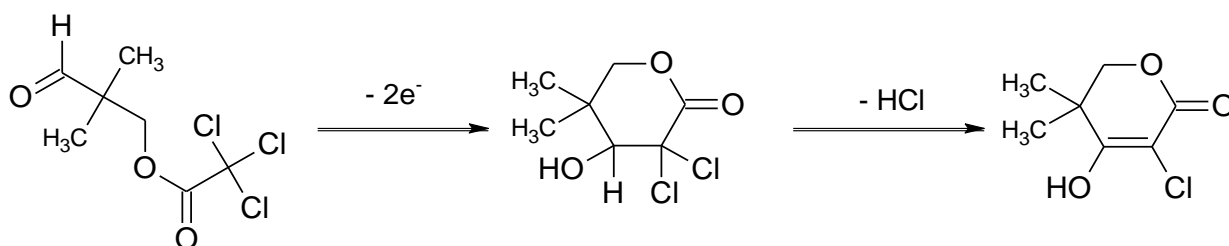
### **5.2.1 ELECTROSYNTHESIS OF 3, 3-DICHLORO-4-HYDROXY-5, 5-DIMETHYL-TETRAHYDROPYRAN-2-ONE**

The reaction yielded a mixture of starting ester and the  $\delta$ -lactones (Fig.19).



**Fig.19** One electron process originated from 2,2-dimethyl-3-oxopropyl trichloroacetate

This way a certain amount of the starting ester remained in reaction mixture due to incomplete reaction. Therefore the definitive process was carried out passing two Faraday per mol (Fig.20).



**Fig.20** Process with two electron passing

### **5.2.2 ELECTROSYNTHESIS OF 3, 3 – DICHLORO - 5,5 – DIETHYL -4-HYDROXYTETRAHYDROPYRAN-2-ONE**

After the first electron has passed and the current decreases partially, the negative potential was increased until -1,2V, so that the intensity decays until zero and the starting material completely disappeared. No pure final products were obtained but a mixture of lactones with two and one chlorine atom. First day the product was liquid but the next day it contained several solid parts. I supposed that the solid part is a rest of salt and therefore I cleaned the mixture with hexane. Solid part was not solved, but after the NMR spectroscopy has been found I find out that the solid is monochlorolactone (Figs 26-28) and spectra of the liquid part agree with dichlorolactone (Figs 22-24). That is why I decided to detect if the time plays a role in the formation of each type of compound. Therefore I separated product of electrolysis to two same parts. The first one I processed same day as electrolysis was terminated and the second was put in the refrigerator overnight and processed the next day.

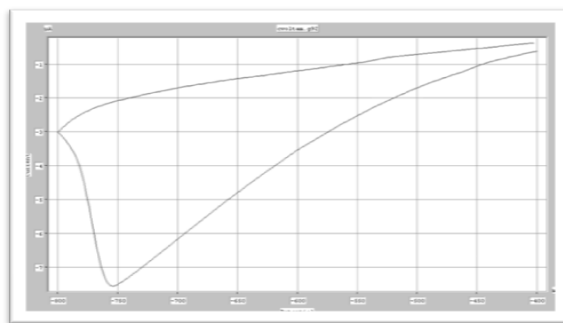
### **5.2.3 ELECTROSYNTHESIS OF 3, 3 – DICHLORO - 5,5 – DIETHYL -4-HYDROXYTETRAHYDROPYRAN-2-ONE OR 3-CHLORO-5, 5 – DIETHYL -4-HYDROXY-5,6- DIHYDROPYRAN -2- ONE**

This reaction I carried out twice. Spectral characteristics of the obtained product with two chlorine atoms (Fig.22) are showed in the following Figs.23, 24, 25. Spectral characteristics of the other obtained product, containing one chlorine and double bond (Fig.26), are showed in Figs.27, 28, 29.

**CV:**

Irreversible reduction peak – 0.75 V

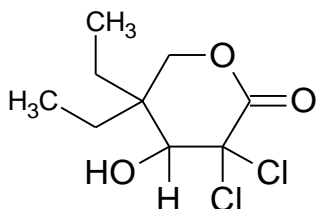
**Fig.21**



**The first part:**

Yield: 0.061g = 0.25mmol = 6.28 %

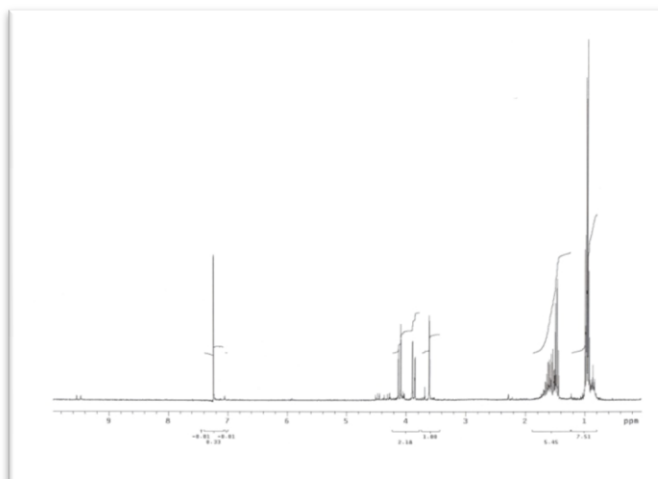
Product was always yellow liquid. NMR showed that this is dichlorolactone (Fig.22).



**Fig.22** 3,3 –dichloro-5,5-diethyl-4-hydroxytetrahydropyran-2-one

**<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>-7.24ppm, 300K ,ppm) Fig.23**

$\delta = 1.19$	(s,1H, -OH)
$\delta = 3.60$	(s,1H,-CH-OH)
$\delta = 3.87$	(d,1H, J=11.2Hz , -CH <sub>2</sub> -)
$\delta = 4.11$	(d,1H, J=11.2Hz , -CH <sub>2</sub> -)
$\delta = 1.63-1.73$	(m,2H,-CH <sub>2</sub> -CH <sub>3</sub> )
$\delta = 1.52-1.62$	(m,2H,-CH <sub>2</sub> -CH <sub>3</sub> )
$\delta = 0.93-0.99$	(m,6H, -CH <sub>2</sub> -CH <sub>3</sub> )





**$^{13}\text{C}$ -NMR ( 75.4 MHz,  $\text{CDCl}_3$  , 300K, ppm)**

$\delta$  =66.69 (-C-OH)

$\delta$  =162.62 (-C=O)

$\delta$  =38.55 (-Cq-)

$\delta$  =24.49 (-CH<sub>2</sub>-CH<sub>3</sub>)

$\delta$  =23.71 (-CH<sub>2</sub>-CH<sub>3</sub>)

$\delta$  =7.50 (-CH<sub>2</sub>-CH<sub>3</sub>)

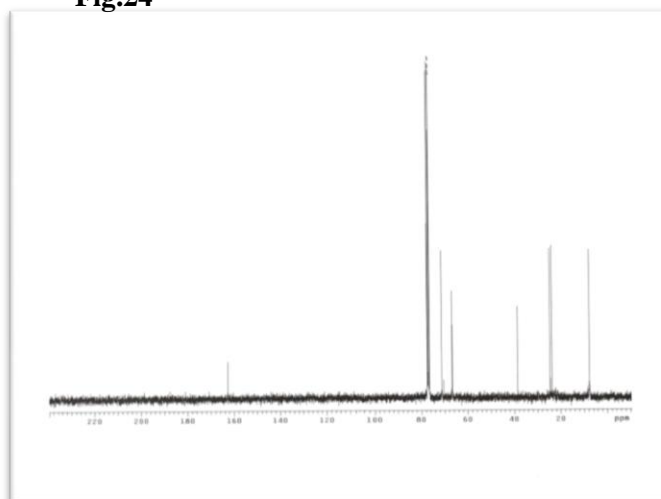
Also signals:

$\delta$  = 70.32

$\delta$  = 71.16

Corresponding to carbons -CH<sub>2</sub>- and -C-Cl<sub>2</sub> .Exact identification of those two signals and the assignig exact values to the carbons need another experimental method.

**Fig.24**



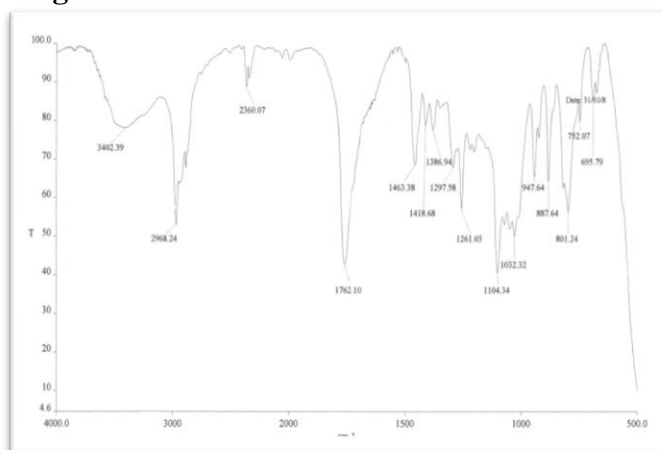
**IR (NaCl, [  $\tilde{\nu}$  cm<sup>-1</sup>])**

$\nu$  = 2972.79 – 2884.34 (C<sub>sp3</sub>-H)

$\nu$  = 1762.10 (C = O)

$\nu$  = 3402.39 (- OH)

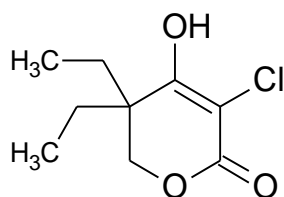
**Fig.25**



**The second part:**

Yield: 0.21g = 0.99 mmol = 24.86 %

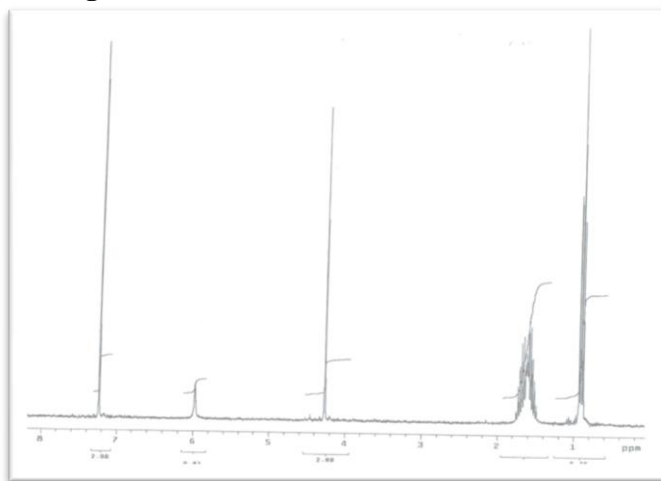
Products were always small white crystals. NMR showed that this is lactone with one chlor and double bond (Fig.26).



**Fig.26** 3-chloro-5,5-diethyl-4-hydroxy-5,6-dihydropyran-2-one

**$^1\text{H-NMR}$  (300MHz,  $\text{CDCl}_3$ -7.24ppm, 300K, ppm ) Fig.27**

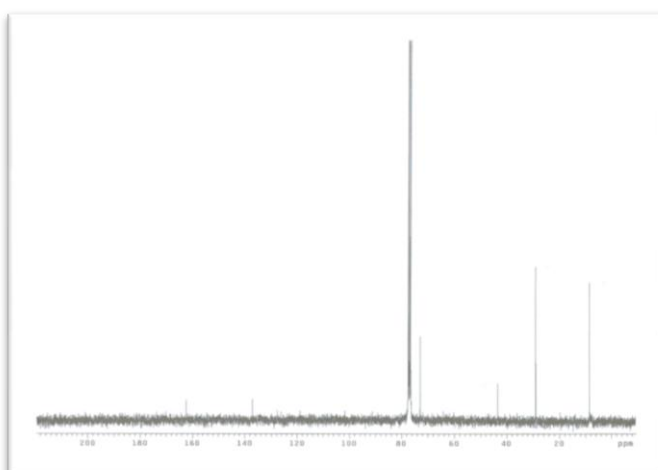
- $\delta = 5.98$  (s, 1H, -OH)
- $\delta = 4.27$  (s, 2H, -CH<sub>2</sub>-)
- $\delta = 1.63\text{-}1.73$  (m, 2H, -CH<sub>2</sub>-CH<sub>3</sub>)
- $\delta = 1.52\text{-}1.62$  (m, 2H, -CH<sub>2</sub>-CH<sub>3</sub>)
- $\delta = 0.89\text{-}0.94$  (m, 6H, -CH<sub>2</sub>-CH<sub>3</sub>)



**$^{13}\text{C-NMR}$  ( 75.4 MHz,  $\text{CDCl}_3$  , 300K, ppm)**

- $\delta = 136.99$  (=C-OH)
- $\delta = 77.20$  (=C-Cl)
- $\delta = 162.31$  (-C=O)
- $\delta = 72.90$  (-CH<sub>2</sub>-O-)
- $\delta = 43.50$  (-Cq-)
- $\delta = 28.96$  (-CH<sub>2</sub>-CH<sub>3</sub>)
- $\delta = 8.48$  (-CH<sub>2</sub>-CH<sub>3</sub>)

**Fig.28**



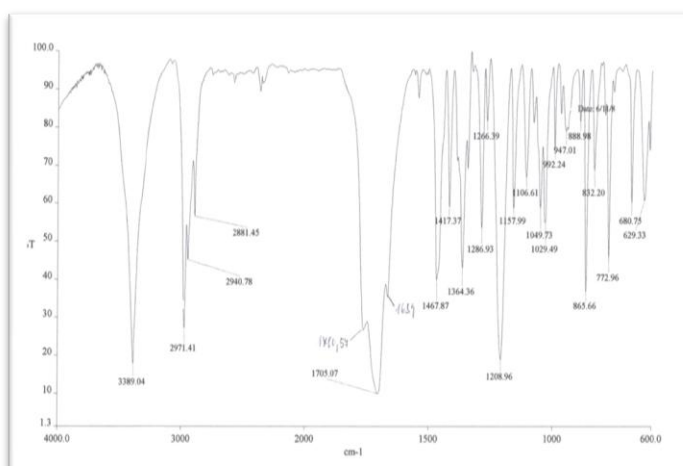
**IR (NaCl, [  $\tilde{\nu}$  cm<sup>-1</sup>])**

$\nu = 2971.41 - 2881.45$  (C<sub>sp3</sub>-H)

$\nu = 1705.07$  (C = O)

$\nu = 3389.04$  (- OH)

**Fig.29**



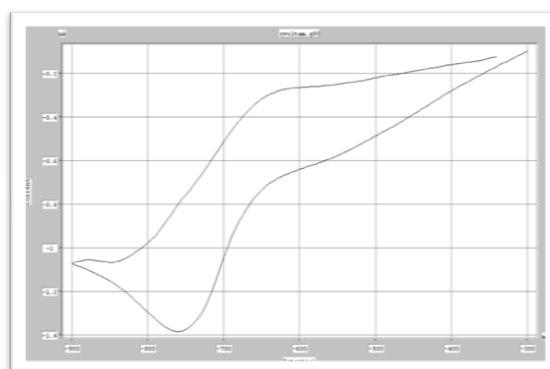
In this case the formation of the different types of products can be connected with the duration of the reaction.

**5.2.4 ELECTROSYNTHESIS OF 3, 3- DICHLORO-4-HYDROXY-5-METHYL-5-PHENYL-TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5-METHYL-5-PHENYL-5,6-DIHYDROPYRAN-2-ONE**

**CV:**

Irreversible reduction peak – 0.75 V

**Fig.30**

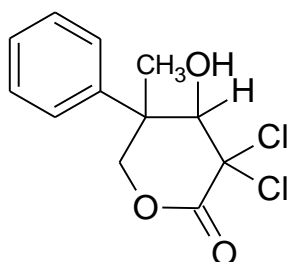


Spectral characteristics of the obtained product with two chlorine atoms (Fig.31) are showed in the following Figs.32, 33, 34. Spectral characteristics of the obtained product with one chlorine and double bond (Fig.35) are showed in Figs.36, 37, 38.

**The first part:**

Yield: 0.54 g = 1.95 mmol = 48.75 %

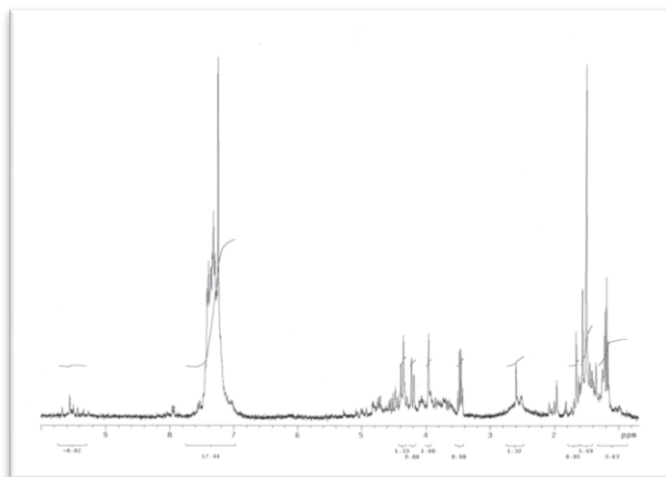
Product was always yellow liquid. NMR showed that this is a mixture of both lactones, but with majority of dichlorolactone (Fig.31). The big molecule and its conformation inhibits total cleaning of the product. The small amount of second product can be always detected in the sample.



**Fig.31** 3,3-dichloro-4-hydroxy-5methyl-5-phenyltetrahydropyran-2-one

**<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>-7.24ppm, 300K , ppm) Fig.32**

δ = 2.60	(s,1H, -OH)
δ = 3.96	(s,1H,-CH-OH)
δ = 4.21	(d,1H, J=11.6Hz ,-CH <sub>2</sub> -)
δ = 4.37	(d,1H, J=11.9Hz ,-CH <sub>2</sub> -)
δ = 7.27-7.41	(m, 5H,-Ph)
δ = 1.51	(s,3H,-CH <sub>3</sub> )



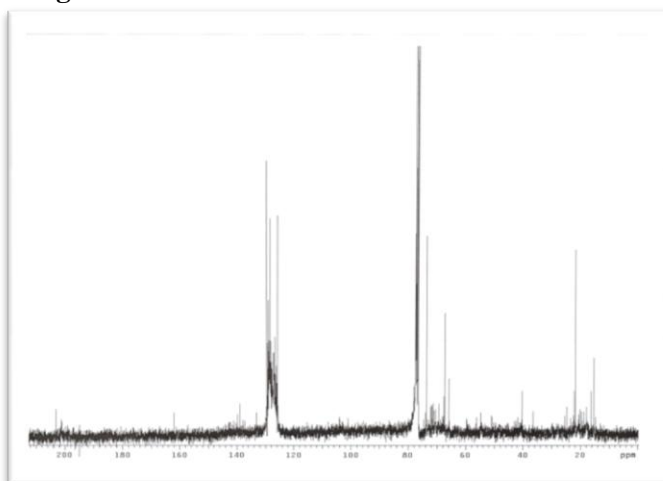
Phenyl ring in the structure of this compound and conformation of whole structure cause that the cleaning process is unsuccessful. Structure always holds a small rest of TEA salt and ether. That is why we can observe signals of those impurities in the spectrum.

**<sup>13</sup>C-NMR ( 75.4 MHz, CDCl<sub>3</sub> , 300K, ppm) Fig.33**

δ =161.89	(-C=O)
δ =73.69	(-CH <sub>2</sub> -O-)
δ =40.08	(-Cq-)
δ =125.7-129.5	(-Ph)
δ =21.68	(-CH <sub>3</sub> )

And signals:

δ =66.01
δ =67.24



Corresponding to carbons **-CH<sub>2</sub>-OH** and **-C-Cl<sub>2</sub>**. Exact identification of those two signals and the assigning exact values to the carbons need another experimental method.

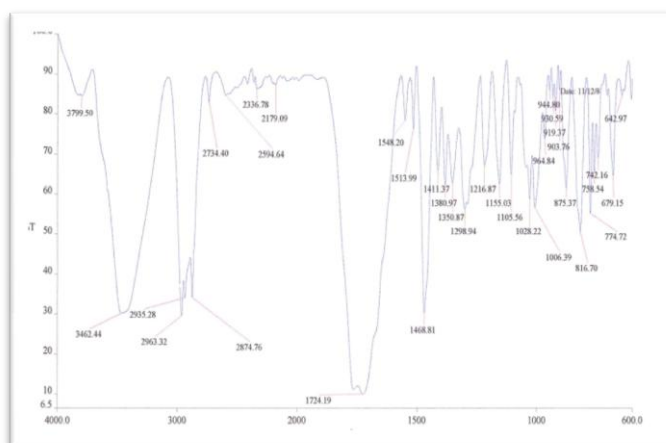
IR (NaCl, [ $\tilde{\nu}$  cm<sup>-1</sup>])

$\nu = 2963.32 - 2874.76$  (C<sub>sp3</sub>-H)

$\nu = 1724.19$  (C = O)

$\nu = 3462.44$  (-OH)

Fig.34



The second part:

Yield: 0.29 g = 1.23 mmol = 30.62 %

Product was also yellow liquid. NMR again showed a mixture of both lactones this once with majority of monochlorolactone (Fig.35).

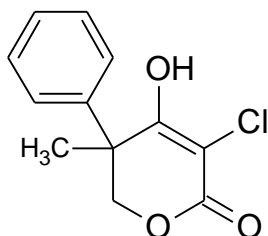
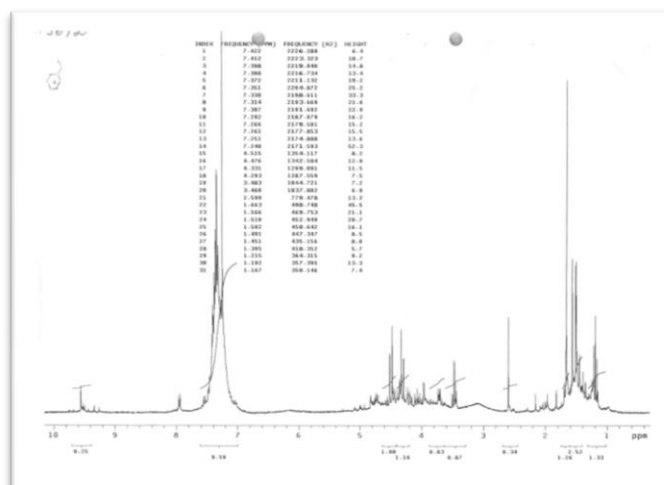


Fig. 35 3-chloro-4-hydroxy-5-methyl-5-phenyl-5,6-dihydropyran-2-one

<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>-7.24ppm, 300K, ppm ) Fig.36

$\delta = 6.01$  (s,1H, -OH)  
 $\delta = 4.50$  (d,1H,J=11.5, -CH<sub>2</sub>-)  
 $\delta = 4.31$  (d,1H,J=11.5, -CH<sub>2</sub>-)  
 $\delta = 7.25-7.41$  (m,5H,Ph)  
 $\delta = 1.66$  (s,3H,-CH<sub>3</sub>)



**$^{13}\text{C}$ -NMR ( 75.4 MHz,  $\text{CDCl}_3$  , 300K, ppm)**

$\delta = 136.13$  ( $=\text{C}-\text{OH}$ )

$\delta = 76.98$  ( $=\text{C}-\text{Cl}$ )

$\delta = 162.48$  ( $-\text{C}=\text{O}$ )

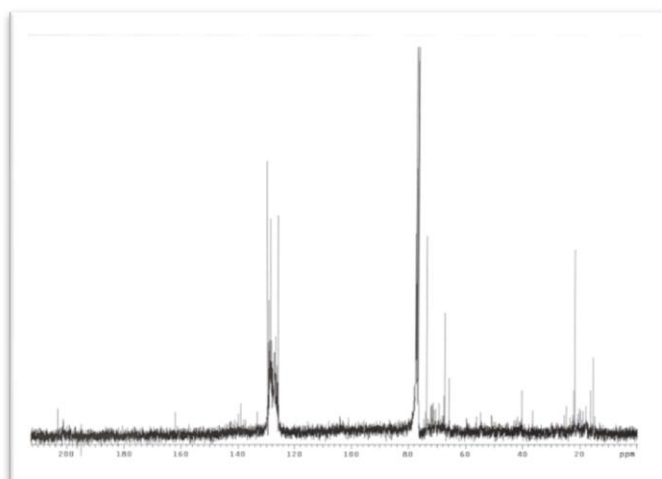
$\delta = 73.63$  ( $-\text{CH}_2-$ )

$\delta = 39.98$  ( $-\text{Cq}-$ )

$\delta = 21.32$  ( $-\text{CH}_3$ )

$\delta = 123.8-127.3$  ( $-\text{Ph}$ )

**Fig. 37**



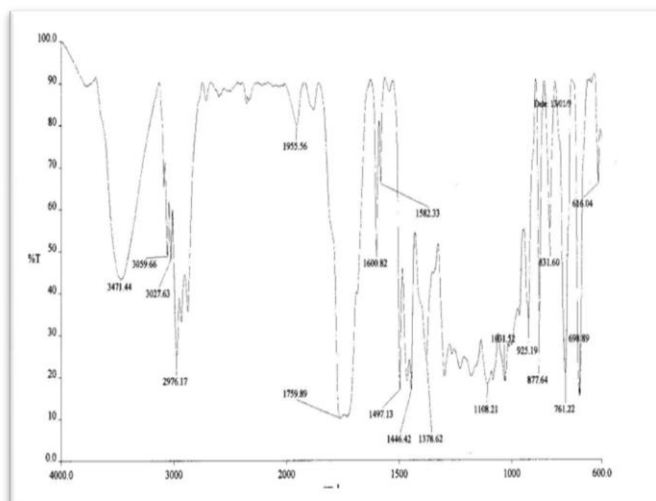
**IR (NaCl, [ $\tilde{\nu}\text{cm}^{-1}$ ])**

$\nu = 2976.17 - 2862.74$  ( $\text{C}_{\text{sp}^3}-\text{H}$ )

$\nu = 1759.95$  ( $\text{C}=\text{O}$ )

$\nu = 3471.44$  ( $-\text{OH}$ )

**Fig.38**



The type of the product evidently connects with duration of the reaction also in this case. It is interesting to observe the liquid state of both types of lactones. While in the cases 5.2.3 and 5.2.5 liquid form corresponds with lactone containing two chlorine atoms, this case is different.

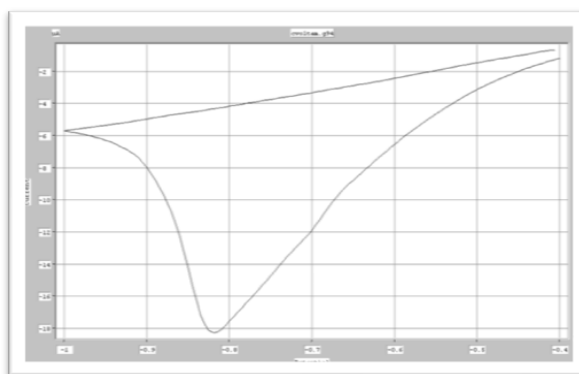
The mesomeric and steric effects inside the phenyl ring inhibit formation of solid state of lactone with one chlorine atom. That is why the product of the reaction of 5.2.4 is always liquid but first part corresponds with dichlorolactone and the second with monochlorolactone.

### 5.2.5 ELECTROSYNTHESIS OF 3,3-DICHLORO-4-HYDROXY-5,5-DIMETHYL-TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5,5-DIMETHYL-5,6-DIHYDROPYRAN-2-ONE

**CV:**

Irreversible reduction peak – 0.80 V

**Fig.39**



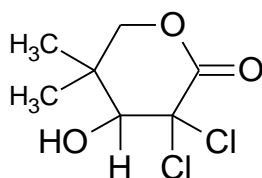
Spectral characteristics of the obtained product with two chlorine atoms (Fig.40) are showed in following Figs.41, 42, 43. Spectral characteristics of the obtained product with one chlorine and double bond (Fig.44) are showed in Figs.45, 46, 47.

**The first part:**

Yield:  $0.19 \text{ g} = 0.90 \text{ mmol} = 22.39 \%$

In the first experiment the product was yellow liquid as I supposed but the second experiment produced white crystals. Third produced also liquid. Again the liquid is the lactone with two chlorine atoms (Fig.40). Rare results in the second experiment can be caused by manual mistake or by some impurities. Or the reaction with this ester doesn't give support to my hypothesis with rider of time in making of each type of lactone.



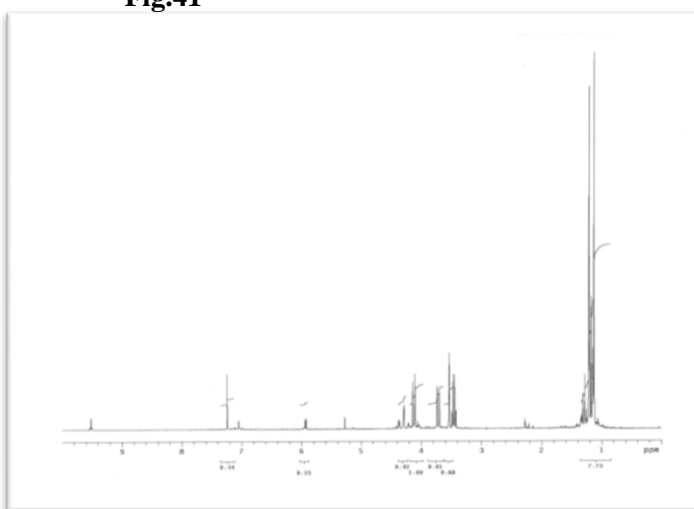


**Fig.40** 3,3-dichloro-4-hydroxy-5,5-dimethyltetrahydropyran-2-one

**$^1\text{H-NMR}$  (300MHz,  $\text{CDCl}_3$ -7.24ppm, 300K )**

$\delta = 1.18$	(s,1H, -OH)
$\delta = 3.54$	(s,1H,-CH-OH)
$\delta = 3.12$	(d,1H, $J=11.5\text{Hz}$ ,-CH <sub>2</sub> -)
$\delta = 4.12$	(d,1H, $J=11.5\text{Hz}$ ,-CH <sub>2</sub> -)
$\delta = 1.21$	(s,6H,-CH <sub>3</sub> )

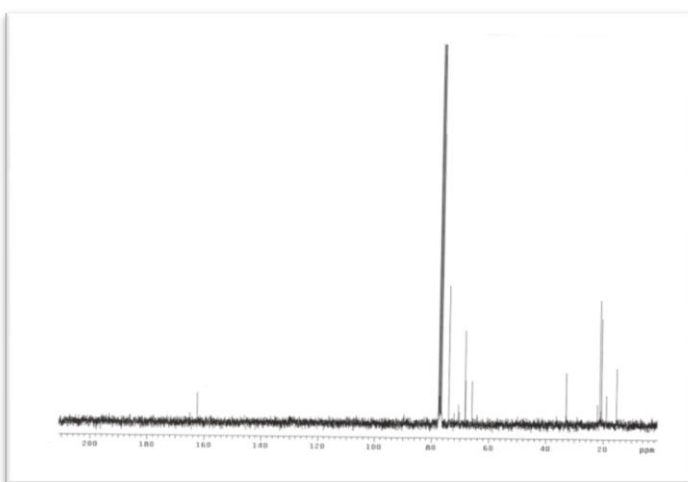
**Fig.41**



**$^{13}\text{C-NMR}$  ( 75.4 MHz,  $\text{CDCl}_3$  , 300K, ppm)**

$\delta = 68.14$	(-C-OH)
$\delta = 70.47$	(-C-Cl <sub>2</sub> )
$\delta = 162.28$	(-C=O)
$\delta = 73.96$	(-CH <sub>2</sub> -)
$\delta = 32.89$	(-Cq-)
$\delta = 21.97$	(-CH <sub>3</sub> )

**Fig.42**



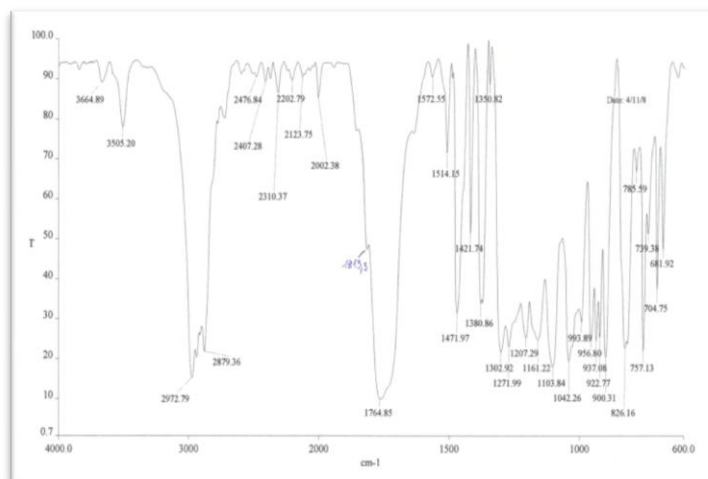
**IR (NaCl, [  $\tilde{\nu}$  cm<sup>-1</sup>])**

$\nu = 2972.79 - 2879.36$  (C<sub>sp3</sub>-H)

$\nu = 1764.85$  (C = O)

$\nu = 3505.20$  (-OH)

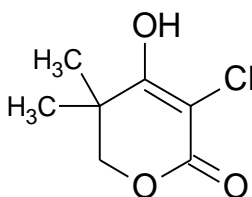
**Fig.43**



**The second part:**

Yield: 0.29 g = 1.62 mmol = 40.56 %

All experiments produced white crystals (Fig.44), i. e. a lactone with one chlorine and double bond.



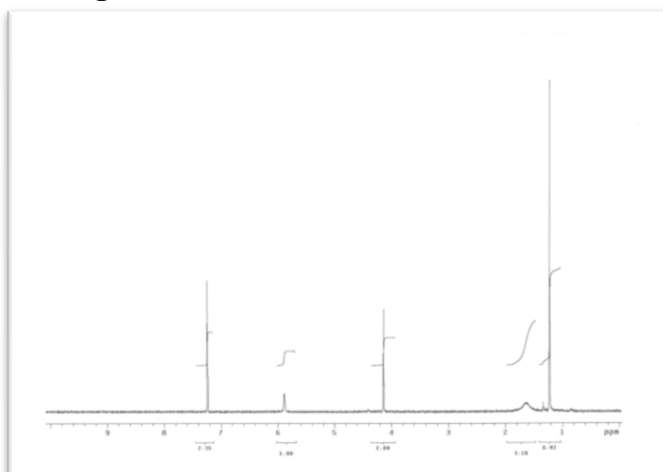
**Fig.44** 3-chloro-4-hydroxy-5,5-dimethyl-5,6-dihydropyran-2-one

**<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>-7.24ppm, 300K, ppm ) Fig.45**

$\delta = 5.88$  (s,1H, -OH)

$\delta = 4.14$  (s,2H, -CH<sub>2</sub>-)

$\delta = 1.23$  (s,6H, -CH<sub>3</sub>)



**$^{13}\text{C}$ -NMR ( 75.4 MHz,  $\text{CDCl}_3$  , 300K, ppm)**

$\delta = 135.32$  ( $=\text{C}-\text{OH}$ )

$\delta = 162.34$  ( $-\text{C}=\text{O}$ )

$\delta = 37.18$  ( $-\text{Cq}-$ )

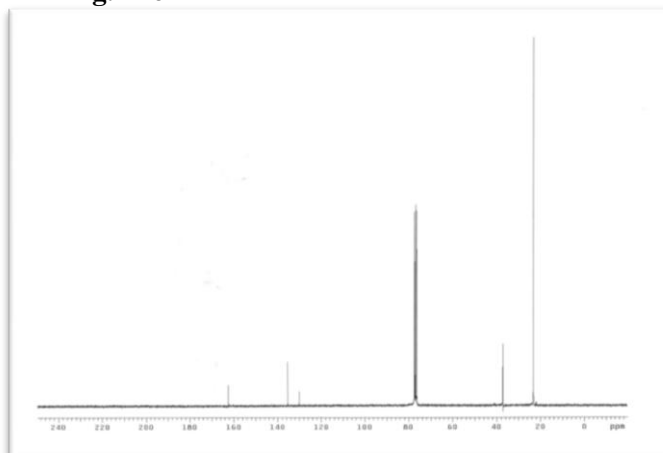
$\delta = 23.20$  ( $-\text{CH}_3$ )

And signals:

$\delta = 77.19$

$\delta = 76.42$

**Fig. 46**



Corresponding to carbons  $-\text{CH}_2-\text{O}-$  and  $=\text{C}-\text{Cl}$ . Exact identification of those two signals and the assignig exact values to the carbons need another experimental method.

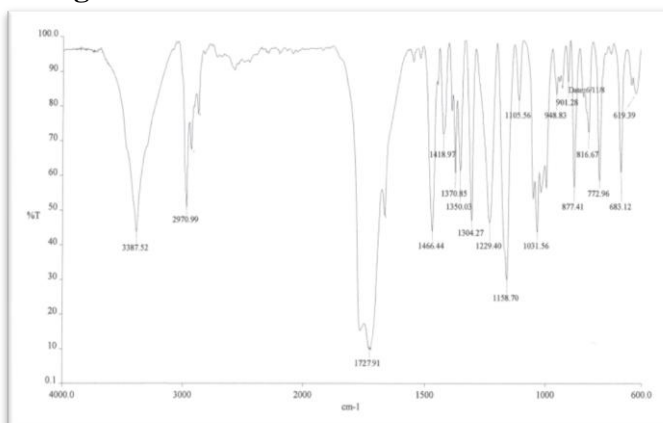
**IR (NaCl,  $[\tilde{\nu} \text{ cm}^{-1}]$ )**

$\nu = 2970.96 - 2873.40$  ( $\text{C}_{\text{sp}^3}-\text{H}$ )

$\nu = 1727.97$  ( $\text{C}=\text{O}$ )

$\nu = 3387.52$  ( $-\text{OH}$ )

**Fig. 47**



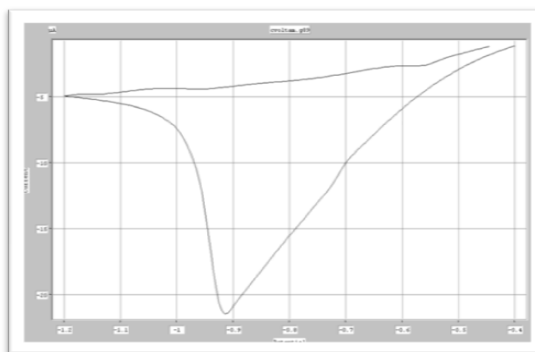
In general we can say that also in this case an influence of the time is possible, but with a small doubtfulness.

### 5.2.6 ELECTROSYNTHESIS OF 3,3-DICHLORO-4-HYDROXY-5-METHYL-5-PROPYL-TETRAHYDROPYRAN-2-ONE OR 3-CHLORO-4-HYDROXY-5-METHYL-5-PROPYL-5,6-DIHYDROPYRAN-2-ONE

CV:

Irreversible reduction peak – 0.90 V

Fig.48

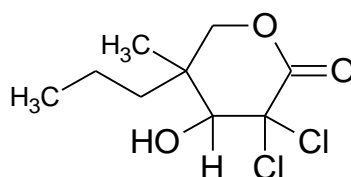


Spectral characteristics of the obtained product with two chlorine atoms (Fig.49) are showed in the following Figs. 50, 51, 52. Spectral characteristics of the obtained product with one chlorine and double bond (Fig.53) are showed in Figs. 54, 55, 56.

**The first part:**

Yield: 0.25 g = 1.01 mmol = 25.58 %

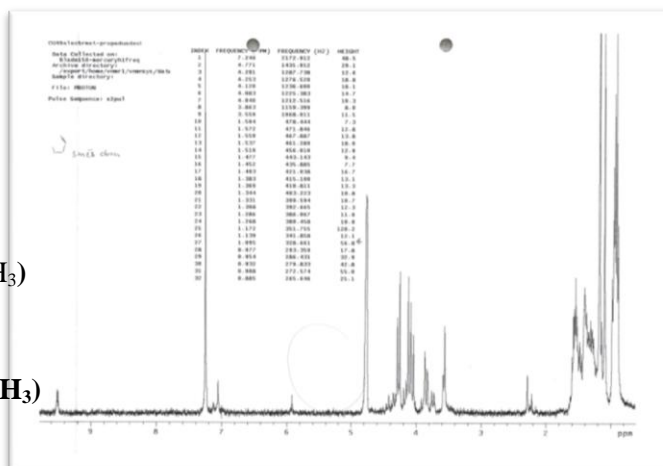
The product is always yellow liquid. It agrees with lactone with two chlorine atoms (Fig.49) (as always first day). Only a minimum amount of the monochlorolactone can be observed.



**Fig. 49** 3,3-dichloro-4-hydroxy-5-methyl-5-propyltetrahydropyran-2-one

**<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>-7.24ppm, 300K ,ppm) Fig.50**

- $\delta = 1.14$  (s,1H, -OH)  
 $\delta = 3.56$  (s,1H,-CH-OH)  
 $\delta = 3.74$  (d,1H, J=11.2Hz ,-CH<sub>2</sub>-)  
 $\delta = 3.84$  (d,1H, J=11.2Hz ,-CH<sub>2</sub>-)  
 $\delta = 1.52-1.57$  (m,2H,J=5.6Hz,-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 1.27-1.48$  (m,2H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 0.91-0.98$  (m,2H, J=7.6Hz, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 1.10$  (s,3H,-CH<sub>3</sub>)



**<sup>13</sup>C-NMR ( 75.4 MHz, CDCl<sub>3</sub> , 300K, ppm)**

**Fig.51**

- $\delta = 68.16$  (-C-OH)  
 $\delta = 162.52$  (-C=O)  
 $\delta = 40.14$  (-Cq-)  
 $\delta = 35.91$  (-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)

Also signals :

- $\delta = 73.60$   
 $\delta = 72.28$

Corresponding to carbons -CH<sub>2</sub>-O- and -C-Cl<sub>2</sub>

And signals:

- $\delta = 18.45$   
 $\delta = 16.65$   
 $\delta = 14.60$

Corresponding to carbons -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>, -CH<sub>3</sub>

Exact identification of those signals and the assignig exact values to the carbons need another experimental method.

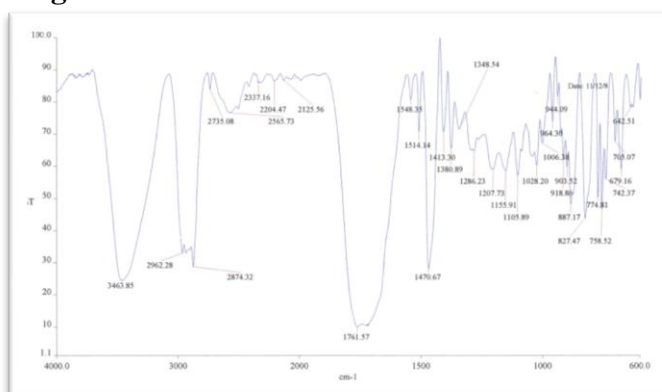
**IR (NaCl, [ $\tilde{\nu}$  cm<sup>-1</sup>])**

**$\nu$  = 2962.11 – 2874.32 (C<sub>sp3</sub>-H)**

**$\nu$  = 1761.37 (C = O)**

**$\nu$  = 3463.85 (- OH)**

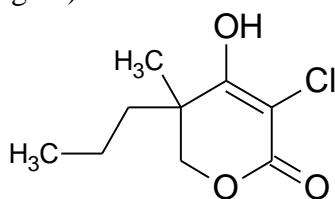
**Fig.52**



**The second part:**

Yield: 0.37 g = 1.82 mmol = 45.48 %

Product is also yellow liquid. But this time the liquid stat corresponds with lactone with one chlorine atom and double bond (Fig.53).



**Fig. 53** 3-chloro-4-hydroxy-5-methyl-5-propyl-5,6-dihydropyran-2-one

**<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>-7.24ppm, 300K, ppm ) Fig.54**

$\delta$  = 5.92 (s,1H, -OH)

$\delta$  = 4.28 (d,1H, J=11.2Hz, -CH<sub>2</sub>-)

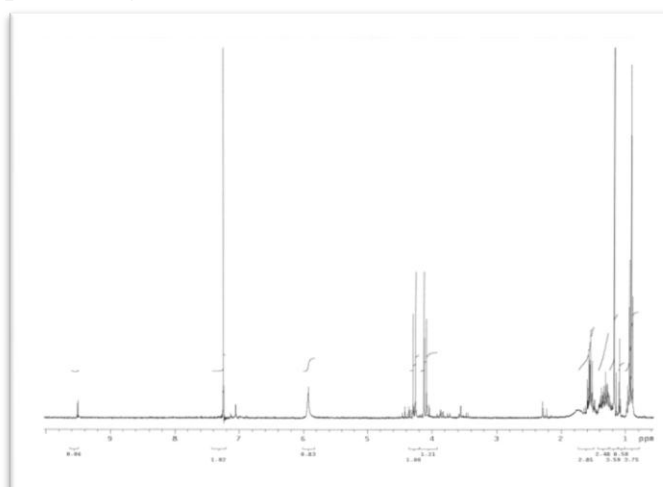
$\delta$  = 4.11 (d,1H, J=11.2Hz, -CH<sub>2</sub>-)

$\delta$  = 1.33-1.35 (m,2H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)

$\delta$  = 1.27-1.30 (m,2H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)

$\delta$  = 0.91-0.96 (m,3H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)

$\delta$  = 1.18 (s, 3H, -CH<sub>3</sub>)



**$^{13}\text{C}$ -NMR ( 75.4 MHz,  $\text{CDCl}_3$  , 300K, ppm)**

**Fig. 55**

$\delta = 135.83$  ( $=\text{C}-\text{OH}$ )  
 $\delta = 77.20$  ( $=\text{C}-\text{Cl}$ )  
 $\delta = 162.37$  ( $-\text{C}=\text{O}$ )  
 $\delta = 74.74$  ( $-\text{CH}_2-$ )  
 $\delta = 21.83$  ( $-\text{CH}_2-\text{CH}_2-\text{CH}_3$ )

And signals:

$\delta = 40.11$

$\delta = 39.25$

Corresponding to carbons  $-\text{Cq}-$  and  $-\text{CH}_2-\text{CH}_2-\text{CH}_3$

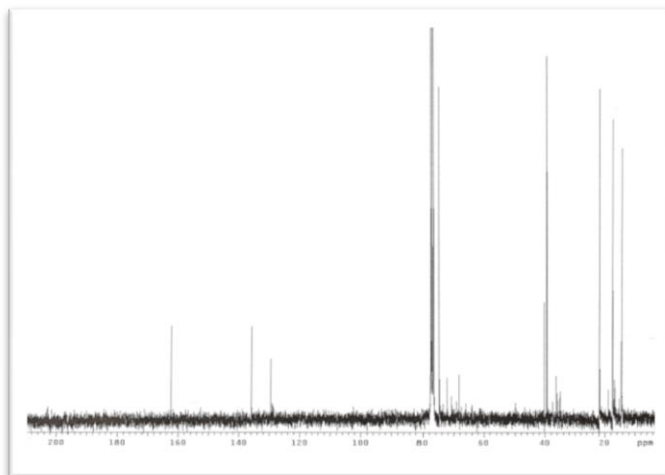
also signals:

$\delta = 17.44$

$\delta = 14.45$

Corresponding to carbons  $-\text{CH}_2-\text{CH}_2-\text{CH}_3$  ,  $-\text{CH}_3$

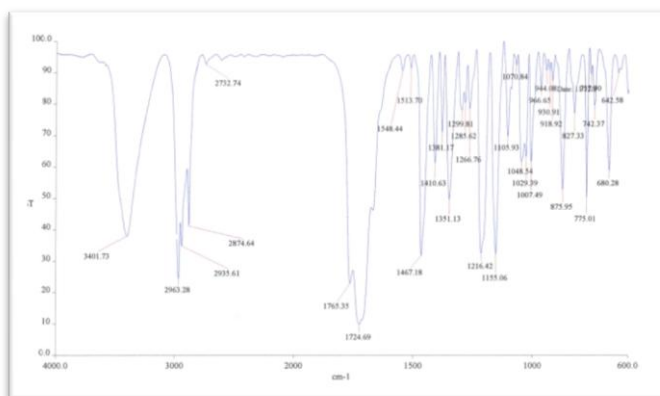
Exact identification of those signals and the assignig exact values to the carbons need another experimental method.



**IR (NaCl, [  $\tilde{\nu} \text{ cm}^{-1}$  ])**

$\nu = 2963.28-2874.64$  ( $\text{C}_{\text{sp}^3}-\text{H}$ )  
 $\nu = 1724.69$  ( $\text{C}=\text{O}$ )  
 $\nu = 3401.73$  ( $-\text{OH}$ )

**Fig.56**



This reaction produced a mixture of both products each day-however the first day with a significant majority of dichlorolactone and the second day with a majority of monochlorolactone. Therefore we can assume even in this case that the time of reaction

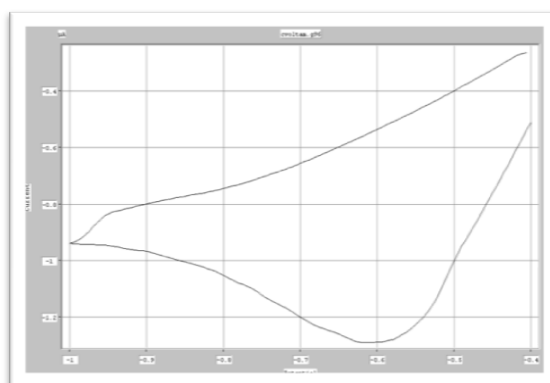
affects formation of the second product. The longer chain of substituents in the position 5 is probably responsible for the liquid state of one chlorolactone under laboratory conditions. On the other hand it is possible that the liquid state is induced by the rest of dichlorolactone in the mixture.

### 5.2.7 ELECTROSYNTHESIS OF 3,3-DICHLORO-5-BUTHYL-5-ETHYL-4-HYDROXYTETRAHYDROPYRAN-2-ONE OR 3-CHLORO-5-BUTHYL-5-ETHYL-4-HYDROXY-5,6-DIHYDROPYRAN-2-ONE

**CV:**

Irreversible reduction peak – 0.60 V

**Fig.57**



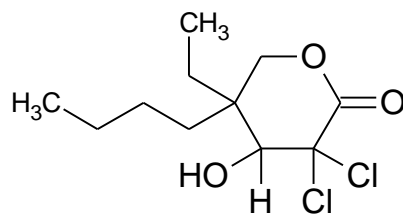
Spectral characteristics of the obtained product with two chlorine atoms (Fig.58) are showed in following Figs. 59, 60, 61, spectral characteristics of the obtained product with one chlorine and double bond (Fig.62) are showed in Figs. 63, 64, 65.

**The first part:**

Yield: 0.58 g = 2.18 mmol = 54.4 %

The obtained yellow liquid is lactone with two chlorine atoms (Fig.58) again. The electrolysis was observed to be slower.

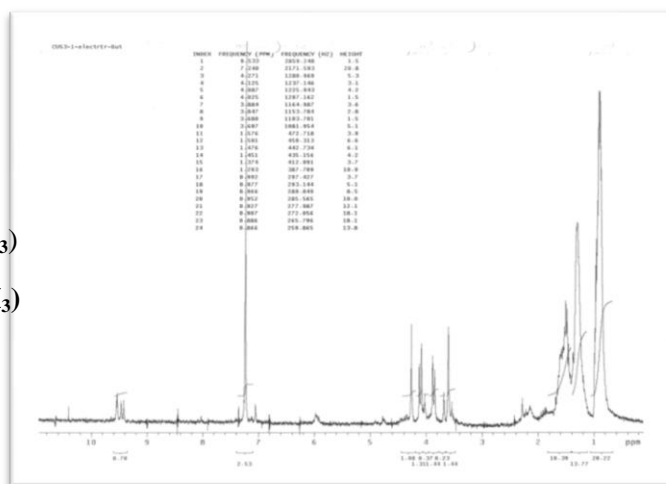




**Fig. 58** 3,3-dichloro-5-buthyl-5-ethyl-4-hydroxytetrahydropyran-2-one

**<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>-7.24ppm, 300K ,ppm) Fig.59**

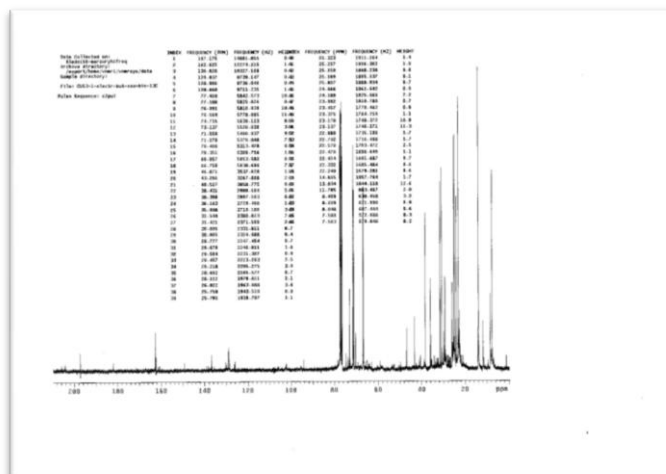
- $\delta = 2.01$  (s,1H, -OH)  
 $\delta = 3.61$  (s,1H,-CH-OH)  
 $\delta = 3.87$  (d,1H, J=10.9Hz ,-CH<sub>2</sub>-)  
 $\delta = 4.11$  (d,1H, J=11.2Hz ,-CH<sub>2</sub>-)  
 $\delta = 0.87-0.95$  (m, 6H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 1.03-1.27$  (m,4H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 1.43-1.61$  (m,4H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 1.43-1.61$  (m,4H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)



**<sup>13</sup>C-NMR ( 75.4 MHz, CDCl<sub>3</sub> , 300K, ppm)**

- $\delta = 67.03$  (-C-OH)  
 $\delta = 162.50$  (-C=O)  
 $\delta = 43.37$  (-Cq-)  
 $\delta = 13.91$  (-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 7.65$  (-CH<sub>2</sub>-CH<sub>3</sub>)

**Fig. 60**



And signals:

$$\delta = 71.84$$

$$\delta = 73.21$$

Corresponding to carbons **-C-Cl<sub>2</sub>**, **-CH<sub>2</sub>-**

Also signals:

$$\delta = 24.25$$

$$\delta = 30.88$$

$$\delta = 26.18$$

$$\delta = 25.22$$

Corresponding to carbons **-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>**, **-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>**, **-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>**, **-CH<sub>2</sub>-CH<sub>3</sub>**

Exact identification of those signals and the assignig exact values to the carbons need another experimental method.

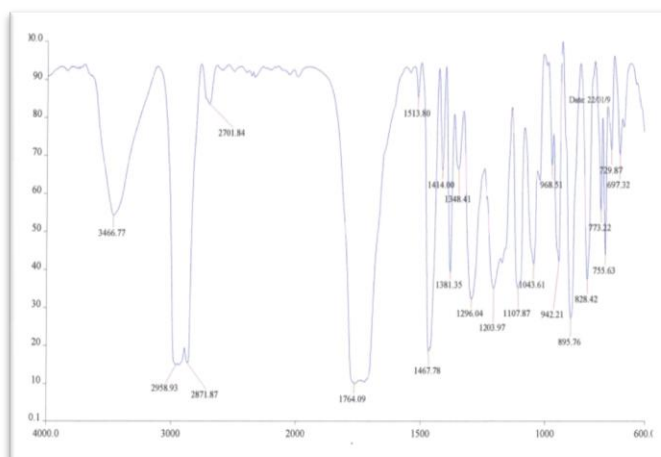
**IR (NaCl, [  $\tilde{\nu}$  cm<sup>-1</sup>])**

$$\nu = 2958.93 - 2871.87 \quad (\text{C}_{\text{sp}^3}\text{-H})$$

$$\nu = 1764.09 \quad (\text{C} = \text{O})$$

$$\nu = 3466.77 \quad (\text{-OH})$$

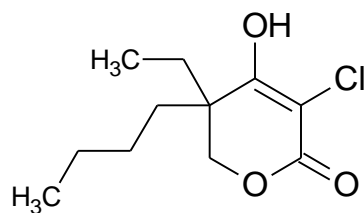
**Fig.61**



**The second part:**

Yield: 0.40 g = 1.72 mmol = 42.96 %

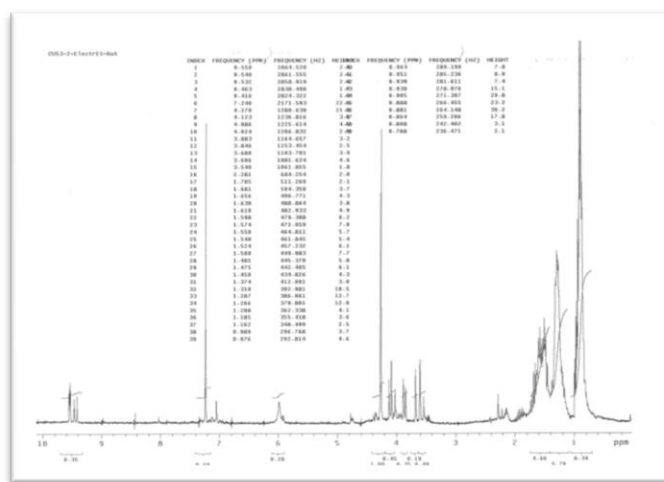
The obtained yellow liquid is lactone with two chlorine atoms (Fig.62) again.



**Fig.62** 3-chloro-5-buthyl-5-ethyl-4-hydroxy-5,6-dihydropyran-2-one

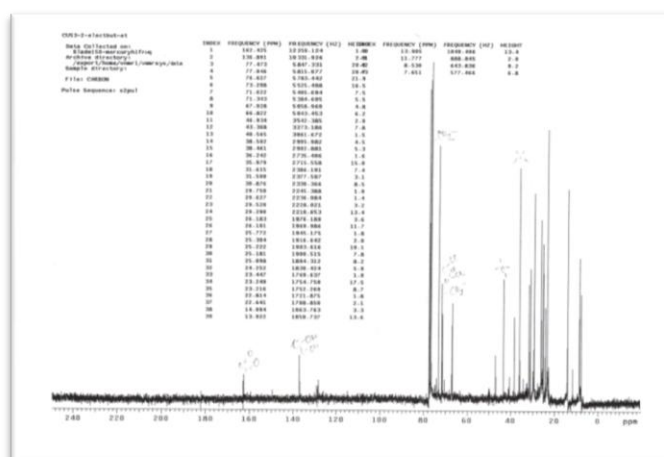
**<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>-7.24ppm, 300K, ppm ) Fig.63**

- $\delta = 5.91$  (s,1H, -OH)  
 $\delta = 4.27$  (s,2H, -CH<sub>2</sub>-)  
 $\delta = 1.43-1.61$  (m,4H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 1.02-1.37$  (m,4H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 0.93-1.00$  (m, 6H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 0.93-1.00$  (m, 6H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)



**<sup>13</sup>C-NMR ( 75.4 MHz, CDCl<sub>3</sub> , 300K, ppm) Fig. 64**

- $\delta = 136.89$  (=C-OH)  
 $\delta = 71.62$  (=C-Cl)  
 $\delta = 162.43$  (-C=O)  
 $\delta = 66.82$  (-CH<sub>2</sub>-)  
 $\delta = 35.98$  (-Cq-)  
 $\delta = 13.92$  (-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)  
 $\delta = 8.53$  (-CH<sub>2</sub>-CH<sub>3</sub>)



And signals:

$$\delta = 23.25$$

$$\delta = 23.22$$

$$\delta = 29.29$$

$$\delta = 26.10$$

Corresponding to carbons **-CH<sub>2</sub>-CH<sub>3</sub>**, **-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>**, **-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>**,  
**-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>**

Exact identification of those signals and the assignig exact values to the carbons need another experimental method.

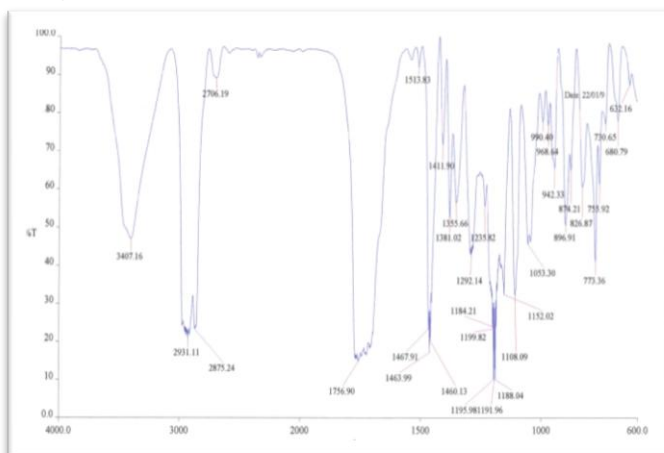
### IR (NaCl, [ $\tilde{\nu}$ cm<sup>-1</sup>])

$$\nu = 2931.11 - 2875.24 \text{ (C}_{\text{sp}^3}\text{-H)}$$

$$\nu = 1756.90 \quad (\text{C}=\text{O})$$

$$\nu = 3407.16 \quad (-\text{OH})$$

**Fig.65**



The hypothesis of the influence of time to the structure of the product was confirmed also in this case. We can again observe (as in reaction 5.2.6) the effect of long chain of substituents in the position 5 influencing the liquid states of both types of lactones.

### 5.3 OVERAL DISCUSION:

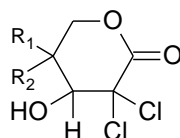
All compounds have been characterized by their spectroscopic properties. IR spectroscopy (Tab.2) presents carbonyl bands at 1725 (monochlorolactones) and 1763  $\text{cm}^{-1}$  (dichlorolactones) (as media values) corresponding to the carboxy group as much as the peaks at 2800  $\text{cm}^{-1}$  (as media values) of  $\text{Csp}^3\text{-H}$  stretch bands and 3400  $\text{cm}^{-1}$  (as media values) of stretch in alcohol group. Aromatic derivates (5a, 5b) also presents  $\text{C}=\text{C}$  stretch bands at 1600, 1582 and 1496  $\text{cm}^{-1}$ .

**Tab.2** Survey of wavenumbers ( $\text{cm}^{-1}$ ) in IR spectra of the obtained lactones.

		$\text{Csp}^3\text{-H}$	$\text{C}=\text{O}$	$\text{-OH}$			$\text{Csp}^3\text{-H}$	$\text{C}=\text{O}$	$\text{-OH}$
<b>1a</b>		2972.79- 2879.36	1764.85	3505.20	<b>1b</b>		2970.96- 2873.40	1727.97	3387.52
<b>2a</b>		2972.79- 2884.34	1762.19	3402.39	<b>2b</b>		2971.41- 2881.45	1705.07	3389.04
<b>3a</b>		2962.11- 2874.32	1761.37	3463.85	<b>3b</b>		2963.28- 2874.64	1724.69	3401.73
<b>4a</b>		2958.93- 2871.87	1764.09	3466.77	<b>4b</b>		2931.11- 2875.24	1756.90	3407.16
<b>5a</b>		2963.32- 2874.76	1724.19	3462.46	<b>5b</b>		2976.17- 2862.74	1759.95	3471.44

$^1\text{H-NMR}$  spectra (Tab.3) of dichlorolactones (**1a-5a**) present the hydroxy peak at  $\delta=1.19$  (**1a-3a**) or 2.00 ppm (**4a, 5a**) and signals corresponding to the aliphatic or aromatic chain. It is very interesting to observe the different types of signals for the methylene group in position 6 of lactones. Two chlorine atoms and only single bonds cause the conformation of the lactones, which is not planar. That is why the two substituents in the position 2 ( $\text{-OH}$ ,  $\text{-H}$ )

effect protons of the methylene group and they are represented by two doublets ( $J_{\text{gem}} = 11\text{Hz}$ ) of the two diastereotopic protons.



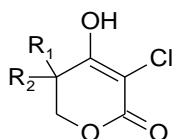
**Fig.66** Dichlorolactone-general structure

**Tab.3** Survey of chemical shifts (ppm) in  $^1\text{H}$ -NMR spectra of the obtained dichlorolactones (Fig.66).

		$\text{R}_1$ -	$\text{R}_2$ -	$-\text{CH}_2-$	$-\text{CH}-$	$\text{OH}-$
<b>1a</b>	$\text{R}_1 = \text{CH}_3$	1.21		3.12,d, $J=11.5\text{Hz}$ ,1H	3.54	1.18
	$\text{R}_2 = \text{CH}_3$	s, 6H		4.12,d, $J=11.2\text{Hz}$ ,1H	s,1H	s,1H
<b>2a</b>	$\text{R}_1 = \text{CH}_2\text{CH}_3$	-CH <sub>2</sub> - 1.63-1.73,m,2H		3.87,d, $J=11.2\text{Hz}$ ,1H	3.60	1.19
	$\text{R}_2 = \text{CH}_2\text{CH}_3$	-CH <sub>2</sub> - 1.52-1.62,m,2H		4.11,d, $J=11.2\text{Hz}$ ,1H	s,1H	s,1H
		-CH <sub>3</sub> ,0.93-0.99,m,6H				
<b>3a</b>	$\text{R}_1 = \text{CH}_3$	1.10	-CH <sub>2</sub> - 1.52-1.57,m,2H	3.74,d, $J=11.2\text{Hz}$ ,1H	3.56	1.14
	$\text{R}_2 = \text{CH}_2\text{CH}_2\text{CH}_3$	s,3H	-CH <sub>2</sub> - 1.27-1.48,m,2H	3.84,d, $J=11.2\text{Hz}$ ,1H	s,1H	S,1H
			CH <sub>3</sub> - 0.91-0.98,m,3H			
<b>4a</b>	$\text{R}_1 = \text{CH}_2\text{CH}_3$	CH <sub>3</sub> - 0.87-0.95,m,6H		3.87,d, $J=10.9\text{Hz}$ ,1H	3.61	2.10
	$\text{R}_2 = (\text{CH}_2)_3\text{CH}_3$	-CH <sub>2</sub> - 1.03-1.27,m,4H		4.11,d, $J=11.2\text{Hz}$ ,1H	s,1H	s,1H
		-CH <sub>2</sub> - 1.43-1.61,m,4H				
<b>5a</b>	$\text{R}_1 = \text{CH}_3$	1.51	7.27-7.41	4.21,d, $J=10.6\text{Hz}$ ,1H	3.96	2.60
	$\text{R}_2 = \text{Ph}$	s,3H	m,5H	4.37,d, $J=10,9\text{Hz}$ ,1H	s,1H	s,1H

$^1\text{H}$ -NMR spectra (Tab.4) of monochlorolactones (**1b-5b**) present the hydroxy peak at  $\delta = 5.90$  ppm and signals corresponding to the aliphatic or aromatic chain. For all those lactones have a plain structure (double bond), we can observe different signals of methylene group in position 6. The signals depend on the substituents  $\text{R}_1$  and  $\text{R}_2$ . If they are identical (**1b**, **2b**), the two protons are represented by singlet at 4.14 ppm (**1b**) or 4.27 ppm (**2b**), whereas in the second case the methylene group presents two doublets ( $J_{\text{gem}} = 11$ ) of the two diastereotopic protons due to the vicinity of the asymmetric carbon atom. Surprisingly the

compound **4b** presents singlet at 4.27 ppm for methylene group in spite of having two different substituents. This phenomenon I observed already in my diploma thesis<sup>1</sup> with esters of trichloroacetic acid. In those two cases (compound **4b** and 2-butyl-2-ethyl-3-oxopropyl trichloroacetate from my diploma thesis) I can state that two long chains (first more than one carbon and second more than two carbons) of substituents ( $R_1$ ,  $R_2$ ) make identical environment and have the same effect to the mentioned methylene group.



**Fig.67** Monochlorolactone-general structure

**Tab.4** Survey of chemical shifts (ppm) in  $^1\text{H}$ -NMR spectra of the obtained monochlorolactones (Fig.67).

		R1	R2	-CH2-	-OH
1b	R1=CH <sub>3</sub>	1.23		4.14	5.88
	R2=CH <sub>3</sub>	s,6H		s,2H	s,1H
2b	R1=CH2CH3	CH3 0.89-0.94,m,3H		4.27	5.98
	R2=CH2CH3	CH2,1.63-1.73,m,2H		s,2H	s,1H
		CH2,1.52-1.62,m,2H			
3b	R1=CH3	1.18	CH3-0.91-0.96,m,3H	4.28,d,J=11.2Hz,1H	5.92
	R2=CH2CH2CH3	s,3H	CH2-1.27-1.30,m,2H	4.11,d,J=11.2Hz,1H	s,1H
			CH2-1.33-1.35,m,2H		
4b	R1=CH2CH3	CH3-0.93-1.00,m,3H		4.27	5.91
	R2=(CH2) <sub>3</sub> CH3	CH2-1.02-1.37,m,4H		s,2H	s,1H
		CH2-1.43-1.61,m,4H			
5b	R1=CH3	1.66	7.25-7.41	4.31,d,J=11.5Hz,1H	6.01
	R2=Ph	s,3H	m,5H	4.50,d,J=11.5Hz,1H	s,1H

$^{13}\text{C}$ -NMR spectra of dichlorolactones (Tab.5) show characteristic signals 162 ppm for lactone group (as media values), 73 ppm (as media values) for methylene group in the

position 6, 70 ppm (as media values) for dichloromethyl, 67 ppm (as media values) for carbon with hydroxy group and values between 32 and 43 ppm for tetrasubstituent carbon.

**Tab.5** Survey of chemical shifts (ppm) in  $^{13}\text{C}$ -NMR spectra of the obtained dichlorolactones (Fig.66).

		R1	R2	Cq	C-OH	C-Cl <sub>2</sub>	CH <sub>2</sub>	C=O
<b>1a</b>	R1=CH <sub>3</sub> R2=CH <sub>3</sub>	21.97		32.89	68.14	70.47	73.96	162.28
<b>2a</b>	R1=CH <sub>2</sub> CH <sub>3</sub> R2=CH <sub>2</sub> CH <sub>3</sub>	CH <sub>3</sub> - 7.50 CH <sub>2</sub> - 24.49 CH <sub>2</sub> -23.71		38.55	66.69	70.32 ↔	71.16	162.62
<b>3a</b>	R1=CH <sub>3</sub> R2=CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	14.60 ↔	CH <sub>3</sub> -16.65 ↕ CH <sub>2</sub> -18.45 ↕ CH <sub>2</sub> -35.91	40.14	68.16	73.60 ↔	72.28	162.52
<b>4a</b>	R1=CH <sub>2</sub> CH <sub>3</sub> R2=(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	CH <sub>3</sub> -7.65 CH <sub>2</sub> -25.22 ↔	CH <sub>3</sub> -13.91 ↕ CH <sub>2</sub> -24.25 ↕ CH <sub>2</sub> -30.88 ↕ CH <sub>2</sub> -26.18	43.37	67.03	71.84 ↔	73.21	162.50
<b>5a</b>	R1=CH <sub>3</sub> R2=Ph	21.68	125.71-129.45	40.08	66.01 ↔	67.24	73.69	161.89

$^{13}\text{C}$ -NMR spectra of monochlorolactones (Tab.6) show characteristic signals 162 ppm for lactone group (as media values), 73 ppm (as media values) for methylene group in the position 6, 77 ppm (as media values) for chloromethyl, 136 ppm (as media values) for carbon with hydroxy group and values between 35 and 43 ppm for tetrasubstituent carbon.



**Tab.6** Survey of chemical shifts (ppm) in  $^{13}\text{C}$ -NMR spectra of the obtained monochlorolactones (Fig.67).

		R1	R2	Cq	CH2	C-Cl	C-OH	C=O
1b	R1=CH <sub>3</sub> R2=CH <sub>3</sub>	23.20		37.18	76.42 ↔ 77.19		135.32	162.34
2b	R1=CH <sub>2</sub> CH <sub>3</sub> R2=CH <sub>2</sub> CH <sub>3</sub>	CH3-8.48 CH2-28.96		43.50	72.90	77.20	136.99	162.31
3b	R1=CH <sub>3</sub> R2=CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	14.45	CH3-17.44 CH2-21.83 CH2-39.25	40.11	74.74	77.20	135.83	162.37
4b	R1=CH <sub>2</sub> CH <sub>3</sub> R2=(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	CH3-8.53 CH2-23.25	CH3-13.92 CH2-23.22 CH2-29.29 CH2-26.10	35.98	66.82	71.62	136.89	162.43
5b	R1=CH <sub>3</sub> R2=Ph	21.32	123.83- 127.31	39.98	73.63	76.98	136.13	162.48

Both  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra include same characteristic signals, also the signals representing the different substituents R1 and R2 .

The question when we can obtain mainly lactones **a** or lactones **b**, if their formation is influenced by the reaction time, was also resolved. Firstly I processed the reaction the same day, immediately after the electrolysis, and this way I prepared the mixture of both lactones. But I observed that if for some reason, I left the solution unprocessed in the refrigerator overnight or over the week end, the next day we could smell clearly the evolution of hydrochloric acid in the flask, and the main product obtained was the monochlorolactone **b**. In order to study the process better I performed all reactions in the uniform conditions: the same electrolysis mixture was divided in two exact parts. One of them was immediately processed and the other was left overnight or longer in the refrigerator. As a result I can conclude that the lactones **a** are formed during the first day mainly, whilst overnight the hydrochloric acid is evolved and the lactones **b** are found in the reaction mixture. The solid molecules of monochlorolactones (5.2.3, 5.2.5) can be easily cleaned by mixing with hexane. However in liquid molecules (5.2.4, 5.2.6, 5.2.7) this method does not be used.

Nagashima and coworkers in their research<sup>34</sup> deal with allyl trichloroacetates but mainly obtained trichlorinated  $\gamma$ -lactones.  $\delta$ -lactones have not been ever observed except for the methallyl trichloroacetate. The ratio between  $\gamma$  and  $\delta$  forms was approximately 4:3; the synthesis in their work was performed under difficult conditions. On the other hand my method is very simple with only 2 steps (electrolysis and cleaning the product). The reaction does not need any special conditions and produces only  $\delta$  forms.

Hu Li and coworkers<sup>33</sup> have synthesized the  $\delta$ -valerolactones with better results. They have synthesized the dihydropyrone derivatives with biological activity against hepatitis C virus, but in complicated way of 6 steps, one of which getting a compound very similar to the lactone with one chlorine and double bond (**b**) prepared by me. The difference is that the substituents are in the  $\delta$ -position contrary to the  $\gamma$ -position as in this thesis. But the main biological activity is fixed to the  $\delta$ -valerolactone structure. That is why we can consider my products to have some mentioned activity.

## **6. CONCLUSION**

In general we can say that in this work the electrochemical reduction of trichloroacetyl esters of aldols is described. The reduction is performed at a controlled potential in dichloromethane/tetraethylammonium chloride on a mercury cathode and it supplies a very simple, clean and economical way to obtain  $\alpha,\alpha$ -dichloro- $\beta$ -hydroxy- $\delta$ -lactones (**a**) with many possibilities of substitution in gamma position with geometrical stereospecificity or alternatively depending on the work up  $\alpha$ - $\beta$  unsaturated  $\alpha$ -chloro- $\beta$ -hydroxy- $\delta$ -lactones-(**b**). Those compounds are obtained with yields between 70-90%.

All the obtained lactones have been characterised by their spectroscopic properties. Thus IR,  $^1\text{H}$ -NMR,  $^{13}\text{C}$ -NMR spectra matched the proposed structures (see results).

The electrochemical properties were studied by cyclic voltammetry. They showed an irreversible reduction peak at voltage range from -0.6 to -0.9 V.

Time experiments showed that the lactones **a** are found during the early stage of reaction and after some small time, commonly overnight, the hydrochloric acid is formed and the lactones **b** appear in the reaction mixture.

There are only two examples of description of this kind of compounds in the literature as was mentioned above. The first is Copper-Catalyzed Cyclization of Allyl Trichloroacetates by Hideo Nagashima and coworkers from Toyahashi (Japan)<sup>34</sup>. The other example is the work made by Hui Li in La Jolla Laboratories of Pfizer<sup>33</sup>.

Very interesting question to the future can be, if the lactone with substituents in  $\gamma$ - position could also have mentioned activity against hepatitis C virus as compounds in work of Hui Li in La Jolla Laboratories of Pfizer<sup>33</sup> with substituents in the  $\delta$ -position or if the method described above can be modified to synthesized lactones with substituents in the  $\delta$ -position.

## **7. LIST OF ABBREVIATIONS**

A	Ampere
CV	cyclic voltammetry
CDCl <sub>3</sub>	chloroform D
d	doublet
DMF	dimethylformamide
ET	electron transfer
Fig	Figure
IR	infrared spectroscopy
K	Kelvin
m	multiplet
M	molar
MHz	megahertz
NMR	nuclear magnetic resonance
Ph	phenyl
Ppm	parts per milion
s	singlet
SCE	saturated calomel electrode
SSE	solvent-supporting electrolyte system
t	triplet
TEAC	tetraethyl ammonium chloride
UME	ultramicroelectrode
V	Volt
$\tilde{\nu}$	wavenumbers
$\delta$	chemical shift

## **8. LITERATURE**

- 
- <sup>1</sup> L. Žáková, Synthesis trichloroacetyl esters of aldols, Diploma thesis 2009, Charles University in Prague, Faculty of Pharmacy in Hradec Králové, Department of Biophysics and Physical Chemistry
- <sup>2</sup> B. Batanero, F. Barba, J. Org. Chem., Electrosynthesis of 3-Chloro-1,4-disubstituted-2(1H)-quinolinones and 3,3-Dichloro-4-hydroxy-1,4-disubstituted-3,4-dihydro-2(1H)-quinolinones, as Well as a New Convenient Process to Dioxindoles, 2003, 68, 3706- 3709.
- <sup>3</sup> Dolly, B. Batanero, F. Barba, Tetrahedron, Cathodic reduction of hydroxycarbonyl compound trichloroacetyl esters, 2003, 59, pp.9161-9165.
- <sup>4</sup> F. Barba, Introducción a la Electroquímica Orgánica, Patronato A. G. Rogel, Murcia, 1975; pp.26-33; C. Uth, Research project, Electroreduction of trichloroacetyl esters of aldols, Universidad de Alcalá, 2002-2003, p.30
- <sup>5</sup> B. Speiser, In Cyclic Voltammetry to Scanning Electrochemical Microscopy: Modern Electroanalytical Methods to Study Organic Compounds, Materials, and Reactions, Current Organic Chemistry, Vol.3 (1999), No. 2, pp.171-186
- <sup>6</sup> F. Martínez-Ortiz, M. L. Alcaraz, I. Roca, M. López-Tenés, Cyclic voltammetry at constant sphericity, Journal of Electroanalytical chemistry 443(1998), pp. 243-252
- <sup>7</sup> J. Hrbas and R. Kohen, Biological Redox Activity, Drug development research 50(2000), pp. 516-527
- <sup>8</sup> M. B. Smith, J. March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure Wiley-Interscience, 5th edition, 2001, ISBN 0-471-58589-0, p.193
- <sup>9</sup> E. Cabaj, D. Kairys, and T. R. Benson Development of a Commercial Process to Produce Oxandrolone John Org. Process Res. Dev.; **2007**; 11(3) pp. 378 - 388
- <sup>10</sup> Organic Syntheses, Coll. Vol. 7(1990), p. 164, Vol. 64(1986), p. 175
- <sup>11</sup> D. Schröder, N. Goldberg, W. Zummack, H. Schwarz, J. C. Poutsma and R.R. Squires, Generation of  $\alpha$ -acetolactone and the acetoxyl diradical  $\bullet\text{CH}_2\text{COO}\bullet$  in the gas phase. International Journal of Mass Spectrometry and Ion Processes, Volumes 165-166 (1997), pp. 71-82.
- <sup>12</sup> Davies-Coleman, M. T., Rivett, D. E.A., Progress in the Chemistry of Organic Natural Products, vol.55(1989), pp. 1-35
- <sup>13</sup> F. Cateni, J. Zilic, M. Zacchigna, P. Bonivento, F. Frausin, V. Scarcia, Synthesis and biological properties of new  $\alpha$ -methylene- $\gamma$ -butyrolactones and  $\alpha,\beta$ -unsaturated  $\delta$ -lactones, European Journal of Medicinal Chemistry 41(2006), pp 192-200
- <sup>14</sup> F. Marion, R. L. Fol, C. Courillon, M. Malacria, Synlett (2001), pp 138-140
- <sup>15</sup> T. Honda, S. Ono, H. Mizutani, K. O. Hallinan, Asymmetry, Tetrahedron, 8(1997), pp.181-184
- <sup>16</sup> M. A. N'Zoutani, A. Pancrazi, J. Ardisson, Synlett (2001), pp.769-772
- <sup>17</sup> Y. Yamashita, S. Saito, H. Ishitani, S. Kobayashi, Journal of American Chemical Society, 125(2003), pp. 3793-3798
- <sup>18</sup> R. A. Singer, E. M. Carreira, Journal of American Chemical Society, 117(1995), pp.12360-12361
- <sup>19</sup> A. B. Ray, M. Gupta, Progress in the Chemistry of Organic Natural Products, vol.63(1994), pp. 1-106



- 
- <sup>20</sup> M.A.N'Zoutani, A. Pancrazi, J. Ardisson, *synlett* 2001, pp. 769-772
- <sup>21</sup> M. Takahashi, *et al.* (1987). "Studies on macrocyclic lactone antibiotics. XI. Anti-mitotic and anti-tubulin activity of new antitumor antibiotics, rhizoxin and its homologues". *J. Antibiot.* **40** (1987): pp. 66–72.
- <sup>22</sup> J.E. Tarver, M.M. Joullie, Synthesis of  $\alpha,\delta$ -unsaturated and  $\delta,\epsilon$ -unsaturated  $\alpha$ -amino acids from Fragmentation of  $\gamma$ - and  $\delta$ -Lactones, *Journal of Organic Chemistry*, vol. 69(2004), pp. 815-820
- <sup>23</sup> A.M. Koskien, L.A. Otsomaa, *Tetrahedron*, vol. 53 (1997), pp. 6473-6484
- <sup>24</sup> L. Wang, P.E. Floreancig, *Organic Letters*, vol. 6(2004), pp. 569-572
- <sup>25</sup> G. Dolladie, L. Gressot, F. Colobert, *Journal of Organic Chemistry*, vol. 39(2000), pp. 357-364
- <sup>26</sup> L. Albrecht, B. Richter, H. Krawczyk, K.A. Jorgensen, *Journal of Organic Chemistry*, vol. 73(2008), pp. 8337-8343
- <sup>27</sup> G. Bluet, B. Bazan-Tejeda, J.M. Campagne, *Organic Letters*, vol. 3(2001), pp. 3807-3810
- <sup>28</sup> J.W. Kramer, Y. Daniel and G.W. Coates, *Organic Letters* vol. 9(2007), pp. 5581-5583
- <sup>29</sup> L.F. Feher, M. Martin, S. Collot-Teixeira, O. Dotsenko, J.L. McGregor, *Current Medical Chemistry*, vol. 13(2006), pp. 3385-3393
- <sup>30</sup> A. Ranganatha, M. Timoney, M. Bycroft, J. Cortes, I.P. Thomas, B. Wilkinson and col., *Chemical Biology*, vol. 6(1999), pp. 731-738
- <sup>31</sup> D.R. Cefalo, A.F. Kiely, M. Wuchrer, J.Y. Jamieson, R.R. Shrock, A.H. Hoveyda, *Journal of American Chemical Society*, vol. 23(2001), pp. 3139-3140
- <sup>32</sup> J. Yang, L. Jia, Q. Hao, et al. "New biodegradable amphiphilic block copolymers of epsilon-caprolactone and delta-valerolactone catalyzed by novel aluminum metal complexes. II. Micellization and solution to gel transition". *Macromolecular bioscience* vol. 5 (2005), pp. 896–903.
- <sup>33</sup> H. Li in *La Jolla Laboratories of Pfizer*, Identification and structure-based optimization of novel dihydropyrones as potent HCV RNA polymerase inhibitors, *Bioorganic & Medicinal Chemistry Letters* vol. 16 (2006), pp. 4834–4838
- <sup>34</sup> H. Nagashima, K. Seki, N. Ozaki, H. Wakamatsu, K. Itoh, Y. Tomo, J. Tsuji, Copper-Catalyzed Cyclization of Allyl Trichloroacetates, *J. Org. Chem.*, 1990, 55 (3), pp 985–990